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CRITICAL APPRAISAL OF GRISEOFULVIN IN DERMATOLOGY*

NORMAN M. WRONG, M.D., F.R.C.P.[C],†
Toronto

A MINIMUM of two years is needed to evaluate a new drug critically. Any drug which embodies a new principle in therapy is usually ushered in with tremendous fanfare, the crowning examples being penicillin and cortisone. Griseofulvin represents a new principle in the treatment of superficial fungous infections and consequently there was tremendous interest in and enthusiasm for it. Fortunately, the original papers all stressed caution in evaluating results and made no sweeping claims.

In the early part of the 20th century, Arthur Whitfield, a British dermatologist, introduced the ointment for the treatment of superficial fungous infections; it still bears his name. Since that time, literally hundreds of so-called cures have been developed by the pharmaceutical houses, by research groups and even by unethical quacks. None of these medications has proved superior to Whitfield's ointment.

In 1955, Wilson[1] stated that the ideal fungicide was an agent that could be given orally, would be non-toxic and would be incorporated into the cells of the skin and produce its fungicidal effect from within outward. His prophecy has been fulfilled, at least in part, by griseofulvin.

In 1939, Oxford, Raistrick and Simonart[2] isolated griseofulvin from *Penicillium griseofulvum dierckx*, but because it had no antibacterial effect it was forgotten. It was revived to attempt to control a fungous disease in plants. J. C. Gentles,[3] a Glasgow bacteriologist, was searching for a treatment for a fungous infection of the feet in Scottish miners when he found that griseofulvin would control a fungous infection experimentally produced in guinea-pigs. His report was published in *Nature* in 1958, and almost immediately Williams[8] in England, Riehl[5] in Austria and Blank and Roth[6] in the U.S.A. obtained supplies for clinical trials on human subjects with resistant fungous infections. Their results were made known late in 1958 and in January 1959, Glaxo-Allenburys (Canada) Ltd. made available to us in Toronto and to other university medical centres in Canada a supply of this antibiotic for experimental use. It has been used by us for over two years and we have sufficient experience with this agent to allow a critical appraisal.

The superficial fungi which infect the human skin[7] and the clinical manifestations of these fungous infections are as follows:

Scalp.—In this country infection of the scalp is almost entirely confined to children before puberty. In this infection, round, scaly lesions are produced, associated with short broken hairs. The causative organisms are: (a) *Microsporum canis*, which commonly affects cats and dogs and is transmitted to children. This infection may result in severe inflammation producing a kerion, which is a boggy, thickened swelling often mistaken for an abscess. The infected hairs give a fluorescence under Wood's light. (b) *Microsporum audouini*, which affects humans only and is transmitted from child to child, and is the organism that has produced epidemics in the past. This infection usually required x-ray depilation for cure up to the time that griseofulvin was introduced, but most cases cleared spontaneously at puberty. Topical treatment is of little avail. There is usually little inflammatory reaction. Infected hairs also fluoresce under Wood's light. (c) *Trichophyton verrucosum*: This is the fungus which is the commonest cause of ringworm in cattle. Farmers and their families may become infected and kerion of the scalp is common. (d) *Trichophyton schoenleini*: This organism causes favus, which affects the scalp of patients at all ages, producing sulphur-colored crusts and permanently bald areas. It is common in eastern Europe and is sometimes seen in immigrants here. Up to the advent of griseofulvin it was almost incurable.

The diseases of the scalp which may be mistaken for fungous infections are: (1) psoriasis, (2) seborrheic dermatitis, (3) alopecia areata, (4) trichotillomania (hair-pulling).

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†Associate Professor of Medicine in charge of Dermatology, University of Toronto.

Glabrous Skin (non-hairy portion)

Excluding the hands, feet and groins, the commonest manifestations are ringed patches tending to clear in the centre, the familiar ringworm.

These lesions may be caused by *Microsporum canis* and by some members of the Trichophyton family, especially *T. rubrum* and *T. verrucosum*, and also by *Epidermophyton floccosum*.

Ringworm of the Bearded Area

This occurs chiefly in farmers and is often caused by *Trichophyton verrucosum*. A very severe inflammatory response results in kerion formation.

Ringworm of the Groin—Tinea Cruris

The fungi usually responsible are *Epidermophyton floccosum* and *Trichophyton rubrum*, which may produce ringed patches tending to clear in the centre.

Other diseases which simulate this disorder are psoriasis, seborrheic dermatitis and intertrigo. It is occasionally seen in minor epidemics in schools and in the armed services but is not very common and the diagnosis is made clinically far too frequently and glibly.

Fungous Infection of Hands

Trichophyton rubrum is the usual causative organism; it produces thickened, red, dry, slightly scaly lesions on the palms and palmar surfaces of the fingers. Nail infection is usually caused by this organism. Finger nails become infected at the sides and the infection spreads across the nail plate, producing opaque, lustreless nails, often with considerable erosion. It does not produce paronychia.

Trichophyton mentagrophytes can also produce nail involvement and occasionally produces ringed lesions on the dorsa of the hands.

Fungous infections of the hands are uncommon, and the diagnosis is made far too frequently and without laboratory confirmation.

Monilia (Candida albicans) can produce chronic paronychia. This is a yeast-like organism, not a true fungus, and is not considered in this group.

Fungous Infection of the Feet

There are three main types:

(a) *The intertriginous types* are seen most commonly between the webs of third and fourth and fourth and fifth toes. This is the commonest fungous infection in humans, and probably 50% of people in this country are so infected. It is manifested by maceration, scaling and fissuring between the toes. It is seen most commonly in hot humid weather, more commonly in the male. A very clever patent medicine catch phrase "athlete's foot" has been applied to this disease. The usual cause is *Trichophyton mentagrophytes*, accounting for at least 90% of the cases. Very infrequently, *Epidermophyton floccosum* is the cause, in less than 5%, so the term epidermophytosis applied to the disease as a whole is an obvious misnomer.

(b) *Vesicular type*. This is seen as grouped vesicles on the soles, the lesion is worse in warm humid weather. It is usually caused by *Trichophyton mentagrophytes*.

(c) *Hyperkeratotic type*. The same manifestations, as seen on the palms, occur on the soles of the feet, red, dry, thickened and slightly scaly lesions. The eruption may easily be missed unless examined in a good light. This is always caused by *Trichophyton rubrum* and may last for years if untreated.

Toe nails may be infected by *Trichophyton rubrum* or *mentagrophytes*; the nails become yellowish, opaque, lustreless and eroded.

Lesions of the feet which are often misdiagnosed and mistreated as fungous infections include the following: eczema—usually affects the dorsa of toes and feet; dyshidrotic eczema—usually affects the soles; psoriasis may affect dorsa or soles of the feet; lichen planus may affect the same areas; periungual warts; hyperhidrosis of the feet is common and frequently misdiagnosed as a fungous infection.

The clinical diagnosis of any fungous infection must always be corroborated by laboratory examination. Specimens of broken hairs, scrapings of skin and nails should be sent to a mycological laboratory. Many such laboratories are operated by provincial departments of health or the larger hospitals. The diagnosis of fungous infections of the scalp, crural region, hands and feet is far too glibly made without laboratory confirmation. Fungicides may make an eczematous eruption worse; and the unnecessary use of griseofulvin for conditions which are not caused by fungus is a waste of the patient's time and money.

Griseofulvin is an antibiotic prepared from the fungus *Penicillium griseofulvum dierckx* and other Penicillia, which inhibits the growth of superficial fungi. It has no effect on the deep fungi or on Monilia (Candida). Given orally in the form of 250 mg. tablets, it is absorbed and finally incorporated into the cells of the epidermis and the hair follicle; it causes distortion and curling of the fungus mycelia which come into contact with it. The agent is not fungicidal but fungistatic.

The dosage for adults is four 250-mg. tablets daily, gradually reduced to three and then two daily. About one-half of this dose is given to children up to the age of 12.

Reactions to griseofulvin: Many thousand patients have been treated in the past 2½ years, and no deaths have been reported. Headache is the most annoying symptom and sometimes is so severe that the drug must be discontinued. Nausea, vomiting and abdominal distension are fairly common and sometimes severe. Dizziness is another annoying symptom, and aircraft pilots should not take the drug while flying. Diminution of the leukocyte count has occurred, but it returns to normal even

while the drug is being taken. Sperm counts do not change during therapy, contrary to early reports of such reactions. Urticaria and mild purpura have been reported, but are never serious.

RESULTS OF THERAPY

Griseofulvin should be ordered only after a positive report of fungous infection has been received from a reliable laboratory.

Microsporum audouini

For infections due to this organism, the dose of griseofulvin recommended is two to four tablets daily for three to four weeks, which together with cutting of infected portions of hair and the use of a topical fungicide results in cure in most cases. Prior to the advent of griseofulvin, only x-ray depilation of the whole scalp or the onset of puberty brought about cure.

Microsporum canis

Sometimes topical fungicides alone will cure the disease. Griseofulvin in dosage mentioned above should be given in all resistant cases.

Trichophyton verrucosum responds only moderately well to griseofulvin, but treatment should be ordered for resistant cases.

Trichophyton schoenleini responds well to griseofulvin. Prior to griseofulvin, results were poor with all treatment, including x-ray depilation.

Ringworm of Beard

This is usually caused by a Trichophyton, usually verrucosum. An inflammatory response causes a boggy swelling simulating an abscess. The application of hot compresses and manual depilation of infected hair are the treatments of choice. Griseofulvin in dosage of four tablets daily may be of some value in controlling the infection.

Glabrous Skin

Typical patches of ringworm are usually caused by *Microsporum canis* but may be caused by some of the Trichophytons. In addition, a low-grade, ringed eruption due to *Trichophyton rubrum* may appear on the buttocks or shoulders or may be very widespread. This latter should be treated with griseofulvin four tablets daily for three to six weeks, but ordinary ringworm can usually be cured in ten days with sulphur ointment or Whitfield's ointment without the necessity for griseofulvin.

Ringworm of Groin (Tinea cruris)

This is often caused by *Epidermophyton floccosum*. Sulphur ointment applied daily or twice daily will usually affect a cure in 10 days without the necessity of griseofulvin. *Trichophyton rubrum* may also cause this condition, and griseofulvin should be given for this infection.

Fungous Infection of the Hands

Hyperkeratotic palms and nail involvement are caused by *Trichophyton rubrum*, and occasionally by *T. mentagrophytes*. The only successful treatment of *T. rubrum* infections of the palms and nails is griseofulvin, four tablets daily for four to six months. Some resistant cases and relapses will be encountered.

Fungous Infection of the Feet

(a) *Intertriginous type*—so-called "athlete's foot"—should be treated by topical treatment only, preferably half-strength sulphur ointment or half-strength Whitfield's ointment at night and mild dusting powder during the day.

Williams[8] has commented he cannot cure this type of lesion even with prolonged griseofulvin therapy.

(b) *Vesicular type*. This is usually caused by *T. mentagrophytes*. Topical remedies will usually control this condition, but prolonged use of griseofulvin may be necessary for cure.

(c) *Hyperkeratotic type*. This type of lesion, characterized by thickened, red, scaly soles and toes with involvement of the nails, is usually caused by *T. rubrum*. It can be helped only by griseofulvin, four tablets daily for six to eight months. Prolonged therapy is necessary because toenails grow so slowly.

T. mentagrophytes may also cause nail infection and should be treated by griseofulvin. The only hope of curing fingernail or toenail fungus infections is by griseofulvin. Surgical avulsion of the nails combined with griseofulvin may accelerate cure, but this is a painful procedure.

Unusual fungous infections of the skin resulting in granulomatous or hyperkeratotic lesions are occasionally seen, more frequently in the tropics and subtropics. The only treatment is prolonged griseofulvin administration, and some of the results have been dramatic in *T. rubrum* and *E. floccosum* infections.

CONCLUSIONS

Griseofulvin given orally embodies a new principle in the treatment of superficial fungous infections.

It has no effect on the deep fungi or on moniliasis, and its effect is variable on members of the superficial group.

It is the only effective treatment for fungous infections of the nails, but must be given in adequate dosage for four to eight months to effect a cure. It is also the only effective treatment for *Trichophyton rubrum* infections of palms and soles.

It is essential that laboratory confirmation of the clinical diagnosis be obtained before treatment is instituted. Griseofulvin is expensive and it is a waste of the patient's time and money to order it for non-fungous infections.

X-ray depilation of the scalp for fungous infection is almost a thing of the past since the introduction of griseofulvin.

Griseofulvin will not cure infections between the toes. Topical treatments are still the best alternative in such cases.

It is hoped that research will develop other antibiotics which may be of superior therapeutic value for superficial fungous infections and may also affect those due to deep fungi.

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SEPTIC SHOCK

L. J. CLEIN, M.R.C.S.(Eng.), L.R.C.P.(Lond.),* and C. M. COUVES, M.D., F.R.C.S.(E.), F.R.C.S.[C], F.A.C.S.,† *Edmonton, Alta.*

IN SPITE of the widespread use of antibiotics, death due to sepsis is still common in surgical patients.[1, 4] The purpose of this paper is to analyze the clinical, laboratory and postmortem data on 33 patients who died with a diagnosis of septic shock.

Endotoxin shock in dogs simulates many of the features of septic shock in humans. In order to investigate new avenues of therapy in septic shock, the endotoxin-shocked dog has been used as a convenient experimental model. Our observations on a new form of therapy carried out in the experimental animal are presented here.

CLINICAL MATERIAL

An analysis of the surgical deaths at the University of Alberta Hospital between January 1, 1956, and December 31, 1960, revealed that 33 patients died of septic shock. Twenty-six patients were male and seven were female. The eldest was 88 years of age and the youngest 18; the average age was 56.8 years. Shock was diagnosed when hypotension first became superimposed upon the infection. The duration of shock in one patient was 11 days; the shortest duration was 12 hours; the average was 4.6 days.

CLINICAL DATA

All patients showed evidence of an infective process. Thirty-two patients had a temperature of 99° F. or higher (Table I). The highest was 109° F.; the lowest 96.2° F.; the average 103° F. The patient in whom the temperature was 96.2° F. had a *Staphylococcus aureus* septicemia and hypotension. In five patients no bacteria were isolated on culture, but all five had hyperpyrexia and leukocytosis. The pulse rate was over 100 in 32 patients; the highest was 170 per minute; the lowest 90 per minute; the average 127. The average leukocyte count in 31 patients was 25,630 with high and low values of 47,800 and 2000 respectively. With the exception of one burned patient in whom it was impossible to record the blood pressure because of the burns, the systolic blood pressure was recorded in every case and prior to death had dropped to 90 mm. Hg or below. The average fall in systolic blood pressure from time of admission to onset of shock was 58 mm. Hg. The value of the CO_2 combining power in mEq./l. in one patient was as low as 4.5; the highest was 30.4 and the average 18.9, showing that acidosis was usually present. The blood urea nitrogen was usually elevated, the mean value being 56 mg. %.

TABLE I.—CLINICAL DATA ON 33 PATIENTS WITH SEPTIC SHOCK

	Maximum	*Minimum*	*Mean*
Age of patient (years)	88	18	56.8
Temperature (°F.)	109	96.2	103
Pulse rate	170	90	127
White blood cell count	47,800	2000	25,630
Hb. (g.%)	19.8	7.0	12.5
CO_2 (mEq./l.)	30.4	4.5	18.9
Blood urea nitrogen (mg. %)	200	8	56

PATHOLOGY AND BACTERIOLOGY

A postmortem examination was carried out in 25 patients. The conditions which were complicated by septic shock are recorded in Table II. Blood culture examinations were done in 17 patients of

TABLE II.—CONDITIONS COMPLICATED BY SEPTIC SHOCK

Condition	*Number*	*Per cent*
Peritonitis	15	45.5
Genitourinary instrumentation	6	18.2
Infected burns	3	9.1
Biliary surgery	3	9.1
Wound infection	2	6.0
Septic abortion	1	
Enterocolitis	1	
		12.1
Cardiac surgery	1	
Gastric surgery	1	

*Canadian Life Insurance Research Fellow.
†Associate Professor of Surgery, University of Alberta.

TABLE III.—POSITIVE BLOOD CULTURES*

Organism	*Number*	*Per cent*
Staph. aureus	6	60
E. coli	2	20
Pr. vulgaris	1	10
Ps. aeruginosa	1	10
Total	10	100

*In 30.3% of patients.

which 10 were positive. Bacteria were isolated by culture from the infected area in 28 patients; and there was a mixed infection in three patients. Peritonitis was present in nearly 50% of the patients in this series in whom septic shock was a complication. This corresponds to the findings of Altemeier and Cole.[1] Genitourinary instrumentation was the next most common causative factor, while infected burns and biliary surgery comprised the majority of the remainder (Tables III and IV).

TABLE IV.—ORGANISMS CULTURED FROM FOCI OF INFECTION

Organisms isolated	*Number of patients*
E. coli	11
Staph. aureus	10
Ps. aeruginosa	3
Cl. welchii	2
Aer. aerogenes	2
Pr. vulgaris	1
Hemolytic streptococcus	1
Candida albicans	1
Total	31

DISCUSSION

The triad of a septic focus, hyperpyrexia and hypotension comprises the syndrome of septic shock. The presence of Gram-negative bacteria in the blood stream is frequently associated with the development of shock.[2] However, the production of shock by a Gram-positive bacteremia is not so well documented. The probable cause of shock complicating sepsis in man is an endotoxin liberated from the cell wall of dead bacteria. The endotoxin is a phosphorus-containing lipopolysaccharide-protein complex which can be isolated and purified by a variety of methods. In the experimental animal the intravenous injection of purified endotoxin produces a syndrome not unlike septic shock in man.

In the present series of cases, supportive therapy for hypotension in the form of noradrenaline or hydrocortisone was administered to 17 patients (51.5%). Noradrenaline was used alone or in conjunction with hydrocortisone in 10 patients, while hydrocortisone was given alone to the remaining seven patients; and 30 of the 33 patients received antibiotics.

Because the syndrome of septic shock is not well recognized, the diagnosis is often not made prior to death. The diagnosis should be considered when a surgical patient with a focus of infection and pyrexia develops hypotension. It is essential to take repeated blood cultures in these patients. A single negative blood culture is not sufficient to rule out the syndrome, while a positive culture will indicate an infection of such severity that the possibility of ensuing shock must be considered.

If the presence of this syndrome is suspected, a number of clinical and laboratory observations must be made: these will include frequent measurements of blood pressure and body temperature, blood cultures, serum electrolytes, pH and CO_2 estimations, urinary output studies, white cell counts and hematocrit measurements.

Intensive treatment directed at the source of infection must be instituted, with supportive treatment including the correction of fluid, electrolyte and pH imbalance; however, there is no standardized treatment for septic shock. Noradrenaline and hydrocortisone should be used, though the rationale for their use is not wholly understood. Because of the wide discrepancy in the methods of treatment in humans and the difficulty of assessing results of therapy in patients, we have attempted to study varying treatments in the endotoxin-shocked dog.

EXPERIMENTAL OBSERVATIONS

In the dog endotoxin is believed to cause shock by producing a widespread vasoconstriction in the smaller arterioles.[5] Among the disturbances in physiology which occur after the administration of this endotoxin are hemorrhagic necrosis of the bowel mucosa, loss of plasma, reduction in the circulatory blood volume, and diminished cardiac output. In order to correct the altered hemodynamics associated with a low cardiac output, a supplemental circulation consisting of an extracorporeal-pump-oxygenator was used at first. However, an assisted circulation alone did not save a great many of these animals from a fatal outcome. In order to reverse the widespread vasoconstriction, phenoxybenzamine hydrochloride (Dibenzyline),* a potent adrenergic blocking agent, was used in addition to the supplemental pump oxygenator. When Dibenzyline is given to dogs intravenously prior to the administration of endotoxin, it prevents death in some animals.[3] However, when given to dogs in established shock it does not influence the fatal outcome. Noradrenaline was not used, as it is known to potentiate endotoxin shock in the experimental animal.[3] The results which follow the use of the combination of Dibenzyline and an assisted circulation have proved to be encouraging.

METHOD

Endotoxin shock was produced in mongrel dogs by the intravenous injection of 5 mg./kg. of purified *E. coli* endotoxin; previous studies indicated that this dose was uniformly fatal. One hour after the injection of endotoxin, treatment was commenced. The blood pressure was monitored throughout by

*Kindly donated by Smith Kline & French Inter-American Corporation, Montreal, Quebec.

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cannulating a femoral artery and connecting it to a mercury manometer. Assisted circulation was provided by cannulating the femoral and jugular veins for the venous component of the system, and the other femoral artery for retrograde arterial perfusion. A sigmamotor pump and disposable plastic bag bubble oxygenator† comprised the pump-oxygenator unit.

Dibenzyline was given intravenously in a dose of 50 mg. diluted in 250 c.c. of glucose and saline. Perfusion was continued for 60 min., during which the Dibenzyline was infused slowly. Thirty-one dogs were used in the experiment and all were subjected to endotoxin shock: thirteen received no treatment and acted as controls; nine received assisted circulation alone; nine received assisted circulation and Dibenzyline.

RESULTS

In the control group all of the dogs died; the average length of survival was 16 hours. In the group receiving assisted circulation alone, the average length of survival was 23 hours, but all the dogs died. In the group receiving assisted circulation and Dibenzyline, the average length of survival in 6 dogs was 37 hours, while 3 were considered to be long-term survivors. All dogs that survived for 24 hours received intramuscular injections of penicillin and streptomycin, and intravenous infusions of glucose and saline. This routine was continued until the dogs died, or were well enough to eat (Table V).

†Pulmo-Pak, Abbott Laboratories.

TABLE V.—RESULTS OF TREATMENT IN EXPERIMENTAL ANIMALS

Number of dogs	*Groups*	*Average length of survival in hours*	*Survivors*
13	No treatment	16	0
9	Assisted circulation alone	23	0
9	Assisted circulation plus Dibenzyline	37	3

SUMMARY AND CONCLUSIONS

The clinical and laboratory data on 33 patients dying on the surgical services of the University of Alberta Hospital with a diagnosis of septic shock would indicate that the development of hypotension is an ominous sign in a patient with a septic focus who has an elevated body temperature.

Repeated blood cultures are essential in the clinical investigation. The existence of a positive culture should alert the clinician to the possibility of the complication of septic shock.

Endotoxin shock in dogs simulates many of the features of septic shock in humans; and the endotoxin-shocked dog is convenient for testing new methods of treatment.

A new form of therapy for endotoxin shock in dogs is described which has given encouraging results.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE PREVENTION OF INSANITY

From the reports of the various Canadian institutions for the insane, I find that there were under treatment at the end of the last fiscal year of the several hospitals, upwards of 12,000 people who were being maintained at the public expense, at a cost, for the year, of nearly $2,000,000. These figures do not take into account those of our insane who are being maintained by private means, nor those who are under care at their homes, in county asylums, poor farms, and other places to which chronic, harmless patients are assigned. It would probably be quite safe to say that there are at least 25,000 insane people in Canada today. Of this number a large majority are not only useless members of society, being unable to earn anything or to contribute in any way to the general weal, but are actually costing the country fully $3,000,000 a year for their support.

Much attention is being given by students of sociology and economics, as well as by those directly associated with the care of the insane, to an apparent increase in the prevalence of insanity. That the number for whom institutional care is being sought is increasing in a much greater ratio than the general population, there can be no doubt. Much of this discrepancy, however, can be accounted for by such factors as the multiplication of institutions for the insane; the facility with which patients may now be transported to such institutions as compared with former times; an increased sensitiveness or intolerance of communities to those exhibiting mental warp; a decreased sense of responsibility on the part of relatives; possibly a lessened dread of asylums; and a growing tendency to voluntary entrance to these institutions. After due allowance is made for such factors, I believe that there is still reason to think that insanity is becoming more common. This is really what we should expect, for the general betterment of hygienic conditions, coupled with a decrease of alcoholism, and possibly also of tuberculosis, has placed restrictions upon nature's methods of eliminating the unfit, and doubtless permits the survival of many who would perish under such conditions as formerly prevailed. Of course, with further advance in preventive medicine, and especially as a result of effort directed particularly to the prevention of insanity, this seeming anomaly will disappear, but, meantime, the demand for institutional accommodation will, no doubt, continue to grow rapidly until practically all mental defectives are provided for.—W. H. Hattie, *Canad. M. A. J.*, 1: 1019, 1911.

INFLUENCE OF DEXTRO-THYROXINE AND ANDROSTERONE ON BLOOD CLOTTING FACTORS AND SERUM CHOLESTEROL IN PATIENTS WITH ATHEROSCLEROSIS*

C. DUFAULT, M.D., G. TREMBLAY, M.D., W. NOWACZYNSKI, D.Sc. and J. GENEST, M.D., F.R.C.P., F.A.C.P., *Montreal*

STUDIES WITH dextro-thyroxine during the last six years have demonstrated that this agent exerts a significant hypocholesterolemic effect with little or no change in the metabolic rate, pulse, and electrocardiographic findings.[1, 2] In 1959, Gallagher and his co-workers[3] demonstrated that administration of tri-iodothyronine increases the excretion of androsterone and etiocholanolone, modifies their urinary ratio and decreases serum cholesterol in patients with hypothyroid and idiopathic hypercholesterolemia. They also showed that intramuscular administration of androsterone lowers serum cholesterol concentration.

Other investigators have shown an increase in *in vitro* blood coagulability during alimentary lipemia[4] and an increased coagulability in atherosclerotic subjects.[5] In addition, blood coagulation has been reported to be increased in hypothyroid and decreased in hyperthyroid conditions.[6] The effect of an anti-coagulant of the dicumarol type on the prothrombin time has been found to be significantly increased in hyperthyroid rabbits and markedly decreased in hypothyroid rabbits.[7] Some evidence has also been presented that coronary atherosclerotic patients have an increased concentration of antihemophilic globulin.[8]

An increase in cephalins in plasma and red cells in atherosclerotic patients was recently demonstrated,[9] and a fall in phospholipids and β-lipoprotein levels was noted in patients receiving dextro-thyroxine.[10]

Several workers have shown that phosphatidyl ethanolamine promotes clotting,[11-14] while phosphatidyl serine either is inactive or exerts an anti-coagulant effect.[13-15]

This paper describes our studies on the effects of the administration of oral dextro-thyroxine and intramuscular androsterone on serum cholesterol, blood coagulation factors, and urinary excretion of androsterone and etiocholanolone of patients with atherosclerosis.

MATERIAL AND METHODS

Thirty-one patients were studied: 13 were men and 18 women. Their ages ranged from 17 to 71 years with an average of 52 years. All female subjects were in their postmenopausal period with the exception of three in whom the tests were performed in the middle of the menstrual cycle.

All patients, with the exception of a 17-year-old girl with a nephrotic syndrome, were atherosclerotic as judged by the following criteria: personal or familial history (peripheral vascular disease, myocardial ischemia, cerebral thrombosis); physical examination (aortic-systolic murmur, retinal artery changes in fundi, palpation of arteries); electrocardiographic signs of coronary ischemia and radiological evidence of dilatation of the aorta with or without calcification. The basal metabolic rate, protein-bound iodine and radioactive iodine^{131} uptake tests were performed in myxedematous patients. Milky or lactescent serum and an increase in serum neutral fats (triglycerides) were the criteria of hyperlipemia. During the study, a group of patients were on a low saturated fat diet* with added corn oil (60 c.c./day), and another group received a fixed diet containing 50% of carbohydrates, 30% of lipids and 20% of proteins.

Twenty-three patients received oral dextro-thyroxine and were arbitrarily divided into four groups.

Group A: Patients with serum cholesterol levels below 250 mg. %: 3

Group B: Patients with serum cholesterol levels above 250 mg. %. 13

Group C: Myxedematous patients: 5

Group D: Myxedematous patients: 2. These patients received thyroid extract (Parke Davis) in a mean dosage of 15 mg./day for six weeks and were used as controls for comparison with patients of group C.

The mean dosage of dextro-thyroxine was 4 to 6 mg./day for a mean duration of 13 weeks, higher dose levels being used for patients with previously untreated spontaneous hypothyroidism.

Eight patients received intramuscular androsterone in a mean dosage of 100 mg./day for 10 days and were similarly divided into three groups:

Group A: Patients with serum cholesterol below 250 mg. %: 4.

Group B: Patients with serum cholesterol above 250 mg. %: 3.

Group C: Myxedematous patient: 1.

The parameters studied were:

A. Blood coagulation: (1) Platelet clumping time (viscous metamorphosis); (2) platelet adhesive index; (3) thromboplastin generation tests: (i) $Al(OH)_3$-treated plasma; this test is a measure of both Factors V (accelerator-globulin) and VIII (antihemophilic globulin or AHG); (ii) Factor IX (Christmas factor or plasma thromboplastin component, PTC) on plasma; (iii) Factor IX (Christmas

*From the Clinical Research Department, Hôtel-Dieu Hospital, Montreal. This work was supported through a grant from the Quebec Heart Foundation, Montreal.

*A diet excluding egg yolk and dairy products such as butter, whole milk, cream, yoghurt, cheese and ice cream; also mayonnaise, spreads containing meat fat, chocolate and meat fats. Meal containing very lean meat (veal, beef, chicken or turkey) was permitted once a day. Fish was permitted *ad libitum*.

factor or plasma thromboplastin component, PTC) on serum; (iv) Platelet activity.

B. Serum cholesterol.

C. Urinary androsterone and etiocholanolone.

From each subject, 50 ml. of blood was collected with a paraffin-coated glass syringe and an 18-gauge stainless-steel needle. Ten ml. of blood was placed in a silicone*-coated glass centrifuge tube at 4° C. This sample was used for determining the platelet clumping time (macroscopic method). Nine ml. of blood was placed in a silicone-coated centrifuge tube in the proportion of nine parts of blood to one part of 3.8% trisodium citrate. This sample was used for the platelet adhesive index (glass wool filter method of Moolten and Vroman),[16] and thromboplastin generation test (method of Biggs and Douglas,[17] modified by Mustard).[18] Serum (non-citrated plasma incubated at 37° C. for five hours) obtained from the remaining blood was used for factor IX and cholesterol determinations.

The method of Abell and co-workers[19] was used for determining serum cholesterol concentration.

For the determination of urinary androsterone and etiocholanolone, a 4- to 6-hour aliquot of complete 24-hour urine collection was used. Urine was extracted with chloroform following incubation with animal β-glucuronidase (300 units per ml. of urine) at pH 4.8 for 72 hours at 37° C. After readjustment to pH 1 with 0.25 H_2SO_4, incubation at room temperature (25° C.) was allowed to proceed for 48 hours. Two additional chloroform extractions were performed at the end of each 24-hour period. After extensive washings of these pooled extracts with 0.1 N NaOH and distilled water, and re-extraction of these washings with $HCCl_3$, the pooled chloroform extracts were dried over 2 g. of anhydrous sodium sulfate per 100 ml. of chloroform extract. These chloroform extracts were evaporated to dryness in a rotary type evaporator* at less than 45° C.

The individual steroids were separated in the Kochakian[20] paper chromatographic system (benzene-cyclohexane (1:1)/propylene glycol-methanol (1:1)), and were located by spraying a strip 0.5 cm. wide with alkaline m-dinitrobenzene solution, a solution of 3 vol. of 2% meta-dinitrobenzene and of 2 vol. of 2.5 N KOH, prepared just before use. The areas corresponding to the standards androsterone and etiocholanolone were eluted with ethanol. The residues from these eluates were dissolved in benzene and chromatographed on an aluminium oxide column (7 x 0.7 cm.). The successive eluents used in amounts of 100 ml. each were: (1) benzene, (2) benzene–0.1% ethanol, (3) benzene–0.5% ethanol. The last eluent was evaporated and the absorption at 515 μ and at 420 μ, after reaction with alkaline m-dinitrobenzene and with the Allen's correction, was measured on a Beckman model DU spectrophotometer.[21, 22]

TABLE I.—DEXTRO-THYROXINE STUDIES (23 PATIENTS)

Groups	*No. pts.*	*Mean serum cholesterol (mg. %)*			*Index of adhesiveness*			*Platelets clumping time (sec.)*		
		Controls (2)	*4-6 mg./day for 13 wk.*	*% change*	*Controls (2)*	*4-6 mg./day for 13 wk.*	*% change*	*Controls (2)*	*4-6 mg./day for 13 wk.*	*% change*
A	3	233 S.E. ±8.5	186† S.E. ±7	−21	1.37 S.E. ±0.05	1.05† S.E. ±0.04	−24	142 S.E. ±19	198* S.E. ±15	+39
B	13	363 S.E. ±19.4	300* S.E. ±15.8	−19	1.34 S.E. ±0.03	1.09† S.E. ±0.016	−19	135 S.E. ±6.7	179† S.E. ±6.0	+32
C	5	412 S.E. ±7.5	234† S.E. ±11.1	−44	1.44 S.E. ±0.06	1.17† S.E. +0.02	−19	134 S.E. ±12.2	204† S.E. ±5.1	+52
D	2	400 S.E. ±54	307 S.E. ±45	−24	1.5 S.E. ±0.14	1.16* S.E. ±0.04	−23	148 S.E. ±30	171 S.E. ±20	+15

Group A: Patients with serum cholesterol below 250 mg. % (3).
Group B: Patients with serum cholesterol above 250 mg. % (13).
Group C: Myxedematous patients (5).
Group D: Myxedematous patients (2).
Thyroid extract (P.D.) mean dosage: 15 mg./day for 6 weeks.

*Difference between control and treated is significant at $.05 \geq p > .01$
†Difference between control and treated is significant at $p \leq .01$

RESULTS

A. *Dextro-thyroxine Studies*

The detailed results obtained from groups receiving dextro-thyroxine are shown in Table I. The main findings are: a fall from the average pre-treatment serum cholesterol of 21%, 19% and 44% in groups A, B and C, respectively; a decrease in platelet adhesive index of 24% in group A, and of 19% in groups B and C; a prolongation in platelet clumping time of 39%, 32% and 52% in groups A, B and C, respectively. The changes in the thromboplastin generation test are indicated in Table II.

A slight but significant decrease in the activity of the $Al(OH)_3$-treated plasma, and of factor IX (PTC or Christmas factor) on serum and plasma

*Dri Film SC-87, General Electric Co.

*Flash evaporator, Laboratory Glass Supply Co., New York 31, N.Y.

TABLE II.—DEXTRO-THYROXINE STUDIES (23 PATIENTS)

Thromboplastin generation test	*Incubation time in min.*	*Group A (3 patients)*				*Group B (13 patients)*				*Group C (5 patients)*				*Group D (2 patients)*			
Activity		*Controls (2)*	*S.E.*	*4-6 mg./day for 13 wk.*	*S.E.*	*Controls (2)*	*S.E.*	*4-6 mg./day for 13 wk.*	*S.E.*	*Controls (2)*	*S.E.*	*4-6 mg./day for 13 wk.*	*S.E.*	*Controls (2)*	*S.E.*	*15 mg./day for 6 wk.*	*S.E.*
$Al(OH)_3$ Treated plasma Clotting time (seconds)	1	42.83	±0.7	48.78†	±1.8	44.32	±0.6	47.91†	±0.78	42.56	±1.6	47.00*	±0.60	40.60	±2.9	49.62	±2.5
	2	17.50	±1.1	19.60*	±0.6	16.80	±0.47	18.98†	±0.40	16.91	±1.5	19.41	±0.52	17.87	±2.4	19.04	±0.9
	3	11.00	±0.6	12.40*	±0.1	11.39	±0.29	12.27*	±0.18	11.31	±0.5	12.58*	±0.18	10.50	±0.3	13.10	±0.8
	4	9.83	±0.3	11.87†	±0.2	10.50	±0.15	11.86†	±0.17	10.56	±0.4	11.88*	±0.16	10.62	±0.3	12.35	±0.4
SERUM IX—P.T.C. Clotting time (seconds)	1	40.66	±1.0	44.52†	±0.8	40.50	±0.98	43.78*	±0.52	38.00	±2.0	43.79*	±0.43	44.25	±5.0	43.29	±3.5
	2	15.41	±0.5	18.14†	±0.7	16.36	±0.62	18.30*	±0.36	15.98	±0.7	19.18†	±0.51	15.00	±1.0	17.50	±2.0
	3	11.16	±0.7	12.17	±1.0	11.38	±0.21	12.00*	±0.20	11.31	±0.6	12.45	±0.22	12.00	±0.6	12.46	±0.3
	4	10.16	±0.2	11.81†	±0.2	10.40	±0.14	11.50†	±0.18	10.61	±0.3	12.14†	±0.24	11.37	±0.5	12.27	±0.17
PLASMA IX—P.T.C. Clotting time (seconds)	1	49.50	±1.1	53.77*	±1.0	50.25	±0.72	54.21†	±0.55	51.76	±1.9	54.19	±0.69	49.75	±3.1	53.97	±1.8
	2	20.33	±2.0	25.92*	±0.4	23.00	±0.38	25.19†	±0.40	23.33	±0.7	24.66	±0.49	21.25	±2.9	24.70	±0.9
	3	12.75	±0.6	15.61*	±1.0	14.09	±0.20	14.94†	±0.14	13.88	±0.5	14.82	±0.24	14.00	±1.0	14.45	±0.6
	4	12.33	±0.7	14.71†	±0.1	13.46	±0.19	14.56†	±0.14	12.96	±0.4	14.29*	±0.25	13.50	±0.8	13.97	±0.7
PLATELETS	1	45.33	±3.3	51.48	±1.0	49.26	±1.10	49.26	±0.87	45.76	±1.3	49.69*	±0.69	44.75	±4.9	50.06	±2.3
	2	22.75	±0.9	22.03	±0.7	22.69	±0.68	21.43	±0.84	21.76	±1.2	21.19	±0.39	21.62	±2.1	24.37	±1.9
Clotting time (seconds)	3	16.50	±0.7	16.25	±1.4	16.90	±0.54	15.44*	±0.26	16.75	±0.5	15.78	±0.31	17.87	±1.0	16.73	±0.6
	4	15.82	±0.8	14.77	±0.4	16.96	±0.39	14.94†	±0.25	16.56	±0.7	15.17	±0.30	17.62	±1.3	15.87	±0.4

GROUP A: Patients with serum cholesterol below 250 mg. % (3).
GROUP B: Patients with serum cholesterol above 250 mg. % (13).
GROUP C: Myxedematous patients (5).
GROUP D: Myxedematous patients (control): 2 patients with thyroid extract (P.D.).
* Difference between "control" and "treated patients" significant at $.01 < p \leq 0.05$.
†Difference between "control" and "treated patients" significant at $p \leq 0.05$.

is observed, as compared with the pre-treatment values. Presumably Hageman or other factors increase in activity during this phase, but we have as yet been unable to dissociate these changes from those of factor IX. In contrast, the platelets appeared more active with a shortening of clotting time.

Urinary androsterone and etiocholanolone were determined in three myxedematous patients. During the control period, the daily combined excretion of androsterone and etiocholanolone was 0.8, 0.1 and 1.1 mg. and increased to 4.0, 2.5 and 2.5 mg. after 60, 20 and 20 days on dextrothyroxine, respectively.

Statistical comparison of these groups has little value because of the marked differences in initial cholesterol levels, the small number of patients and the differences in age. Nevertheless, the fall in serum cholesterol and the prolongation of platelet clumping time expressed as per cent change from control values are more marked in myxedematous group C than in euthyroid groups A and B, although the platelet adhesive index did not show such a marked difference in all three groups.

In the thromboplastin generation test, at the third and fourth minute of incubation, the differences in clotting time between these groups were not significant. Usually, the changes in these tests first appeared two or four weeks after the beginning of therapy, with a peak at about the sixth or eighth week.

The trends of these various parameters before and during dextrothyroxine administration in these patients warrant illustration in individual cases.

Fig. 1 shows the changes in serum cholesterol, platelet adhesive index, platelet clumping time, clotting time of $Al(OH)_3$-treated plasma and of Factor IX (on serum at the fourth minute of incubation), in a 55-year-old man with a history of renal hypertension. Angiography revealed a narrowing due to an atheromatous plaque in the left renal artery. Moderate arteriosclerotic changes were seen on examination of the fundi and a systolic aortic murmur was heard on auscultation. The roent-

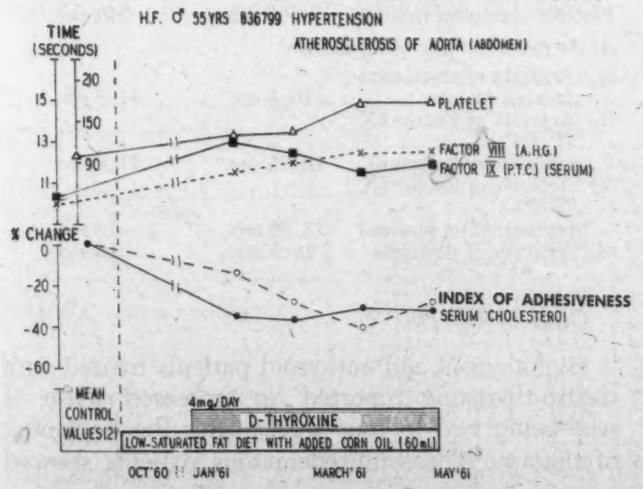

Fig. 1.—Effects of d-thyroxine given for four months at 4 mg./day to a hypertensive patient on platelet clumping time (△—△) expressed in seconds, $Al(OH)_3$-treated plasma (x- - - -x) and factor IX (P.T.C. or Christmas) of serum (■—■) expressed in seconds at the fourth minute of incubation, index of adhesiveness (o- - - -o) and serum cholesterol (●—●) expressed in per cent change from control values.

TABLE III.—PATIENT H.F., B36799, 55 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (4) (18 weeks)*
Serum cholesterol	245 mg. %	168 mg. %
Platelet adhesive index	1.5	1.07
Platelet clumping time	97 sec.	154 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma)	10 sec.	12.12 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	10.75 sec.	15.4 sec.
(d) Activity of platelets	16.5 sec.	15.4 sec.

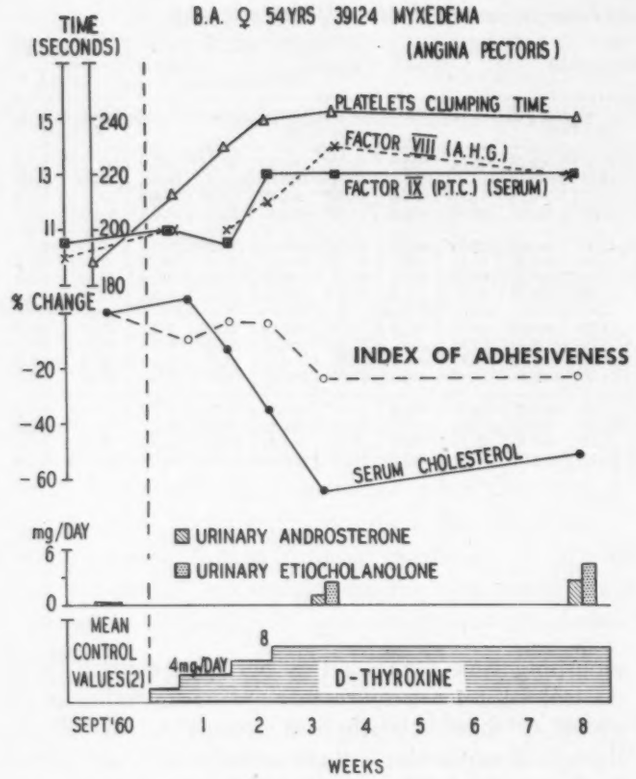

Fig. 2.—Effects of d-thyroxine given for eight weeks at a mean dosage of 6 mg./day to a myxedematous patient on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

genogram of the chest showed dilatation of the aorta with left ventricular hypertrophy. This patient received d-thyroxine for a period of four months at 4 mg./day. The detailed results are given in Table III.

Fig. 2 illustrates similar changes in a 54-year-old myxedematous woman, described in detail in Table IV. This patient had a history of myxedema of five years' duration: sensitivity to cold, puffiness of the face, eyelids and hands, and repeated attacks of angina pectoris and dyspnea on exertion. On physical examination, the speech was slow and the voice had a deep tone. Drowsiness, dry and thickened

TABLE IV.—PATIENT B.A., B39124, 54 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (5) (8 weeks)*
Serum cholesterol	385 mg. %	261 mg. %
Platelet adhesive index	1.45	1.26
Platelet clumping time	188 sec.	232 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10 sec.	12.2 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.5 sec.	12.1 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	12 sec.	13 sec.
(d) Activity of platelets	18 sec.	16 sec.
Sum of urinary androsterone and etiocholanolone	0.8 mg./day	4.0 mg./day*

*Average of four 24-hour period values.

skin, and bradycardia at 60 beats per minute were also noted. Her basal metabolic rate was −25, radioactive iodine^{131} uptake was 3.4% after 24 hours, and P.B.I. was 3.3 μg. %. After five weeks of administration of d-thyroxine, the anginal pains were less severe in intensity and frequency.

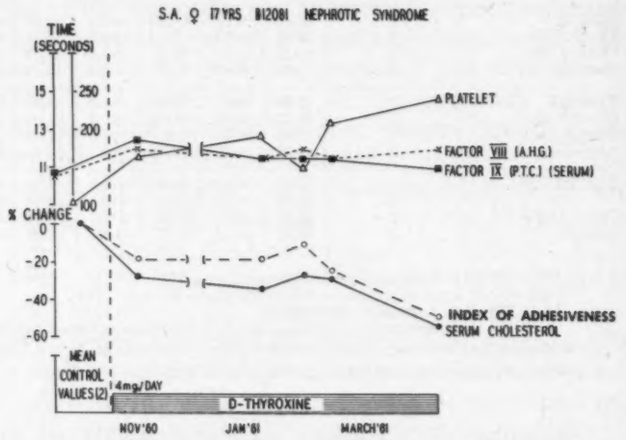

Fig. 3.—Effects of d-thyroxine given for six months at 4 mg./day to a 17-year-old girl with a nephrotic syndrome on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

The results obtained in a 17-year-old girl with a nephrotic syndrome are shown in Fig. 3. In this hypercholesterolemic patient, the trend of changes in serum cholesterol, platelet adhesive index, platelet clumping time and plasma thromboplastin time are the same as in atherosclerotic patients. The detailed results are given in Table V. After 24 weeks on dextro-thyroxine, serum neutral fats showed a significant decrease.

TABLE V.—PATIENT S.A., B12081, 17 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (5) (24 weeks)*
Serum cholesterol	674 mg. %	457 mg. %
Platelet adhesive index	1.45	1.15
Platelet clumping time	100 sec.	192 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10.5 sec.	11.8 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.75 sec.	11.6 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	13.75 sec.	14 sec.
(d) Activity of platelets	18.5 sec.	15 sec.

Clinical Effects

Hypothyroid and euthyroid patients treated with dextro-thyroxine reported an increased sense of well-being two to four weeks after the beginning of therapy. Three myxedematous patients showed a rapid loss of weight and decrease in asthenia.

One hypothyroid and five euthyroid patients observed a reduction in intensity and frequency of anginal attacks. One subject suffering from angina

TABLE VI.—ANDROSTERONE STUDIES (8 PATIENTS)

Groups	No. pts.	Mean serum cholesterol (mg. %)			Index of adhesiveness			Platelet clumping time (sec.)		
		Controls (2)	10 mg./day for 10 days	% change	Controls (2)	100 mg./day for 10 days	% change	Controls (2)	100 mg./day for 10 days	% change
A	4	187 S.E. ±9	159 S.E. ±14	−16	1.45 S.E. ±0.04	1.24* S.E. ±0.07	−15	144 S.E. ±7.5	182* S.E. ±14.0	+26
B	3	253 S.E. ±20	194* S.E. ±16	−24	1.43 S.E. ±0.07	1.28 S.E. ±0.07	−11	136 S.E. ±12	186† S.E. ±8.4	+36
C	1	521	346	−34	1.3	1.19	−9	127	210	+57

Group A: Patients with serum cholesterol below 250 mg. % (4).
Group B: Patients with serum cholesterol above 250 mg. % (3).
Group C: Myxedematous patient (1).

*Difference between control and treated is significant at $.05 \geq p > .01$
†Difference between control and treated is significant at $p \leq .01$

attacks manifested no clinical improvement with the medication.

No side effects were noted during this study. We observed no thyrotoxic effects, except in a euthyroid patient who received 12 mg. of dextro-thyroxine per day for 11 weeks and manifested nervousness, tremors and diaphoresis. No escape phenomena in the various tests occurred during the therapy.

For comparison, thyroid extract (Parke Davis) was given to two myxedematous patients with a daily mean dosage of 15 mg. for six weeks (Group D). Changes of the same degree and in the same direction were observed as in those patients treated with dextro-thyroxine administration.

The percentage of variations were −24%, −23% and +15% for serum cholesterol, platelet adhesive index and platelet clumping time, respectively. The thromboplastin generation test showed the same trends as in the dextro-thyroxine group.

B. *Androsterone Studies* (Table VI)

Androsterone administration resulted in a fall from average pretreatment serum cholesterol values of 16%, 24% and 34% for groups A, B and C, respectively. No significant difference in platelet adhesive index in the three groups was noted, but we observed a marked prolongation of platelet clumping time in group C as compared with that in groups A and B. Nevertheless, a statistical approach is quite difficult, because of the small number[8] of patients studied.

In the thromboplastin generation test, at the third and fourth minute of incubation, we noticed in all groups except group A, the same trend as in the dextro-thyroxine group (Table VII). In group A, the changes were not significant. These discrepancies may be explained by the fact that therapy had to be stopped in two of the four group A patients because the injections became too painful.

Fig. 4 illustrates the changes obtained in a 48-year-old euthyroid man suffering from repeated attacks of angina pectoris on exertion with dyspnea and sweating. This patient has a history of attacks of angina pectoris. Pain was promptly relieved by nitroglycerin. The physical examination showed moderate arteriosclerotic changes in fundi and a systolic aortic murmur. Dilatation of aorta was present on the teleroentgenogram of the heart. No improvement of angina occurred during medication. A significant fall in serum cholesterol, a decrease

TABLE VII.—ANDROSTERONE STUDIES (8 PATIENTS)

Thromboplastin generation test	Incubation time in min.	Group A (4 patients)				Group B (3 patients)				Group C (1 patient)			
Activity		Controls (2) S.E.		100 mg./day S.E. for 10 days		Controls (2) S.E.		100 mg./day S.E. for 10 days		Controls(2) S.E.		100 mg./day S.E. for 10 days	
$Al(OH)_3$ treated plasma clotting time (sec.)	1	45.75	±2.1	45.50	±2.2	39.58	±3.6	45.43	±1.6	53.00		46.30*	
	2	18.12	±0.6	19.37	±1.0	15.50	±1.2	18.68*	±0.8	17.50		23.00	
	3	12.06	±0.4	12.37	±0.4	11.25	±0.4	12.16	±0.6	10.50		12.50	
	4	10.68	±0.13	11.18	±0.6	9.58	±0.45	11.41*	±0.55	9.25		11.60	
Serum IX—P.T.C. clotting time (sec.)	1	41.50	±2.0	43.62	±1.4	40.16	±1.8	42.00	±1.3	41.50		42.00	
	2	16.68	±0.6	19.12	±2.1	14.75	±1.0	18.20*	±1.4	14.50		21.60*	
	3	11.75	±0.5	12.06	±0.5	10.83	±0.7	12.05	±0.7	11.25		13.30	
	4	10.50	±0.4	11.06	±0.5	9.83	±0.5	11.47*	±0.55	10.25		12.00	
Plasma IX—P.T.C. clotting time (sec.)	1	48.18	±0.9	49.25	±1.2	52.33	±1.8	54.50	±1.7	52.00		52.30	
	2	22.31	±1.3	22.37*	±1.1	23.16	±1.2	23.83	±0.7	23.50		25.60	
	3	13.50	±0.5	13.62	±0.5	14.00	±0.7	13.91	±0.7	14.50		14.80	
	4	12.62	±0.5	12.80	±0.5	13.08	±0.6	13.33	±0.7	12.25		13.60	
Platelets Clotting time (sec.)	1	45.25	±3.4	48.87	±1.1	48.83	±1.2	47.76	±2.1	42.50		48.00	
	2	20.75	±1.1	21.12	±0.5	25.00	±1.5	19.60*	±1.1	20.50		18.60	
	3	15.93	±0.8	16.12	±0.5	16.58	±0.6	15.93	±0.7	17.50		15.00	
	4	15.25	±0.6	15.25*	±0.7	17.50	±0.5	15.68*	±0.55	17.25		14.60	

Group A: Patients with serum cholesterol below 250 mg. % (4).
Group B: Patients with serum cholesterol above 250 mg. % (3).
Group C: Myxedematous patient (1).

*Difference between "control" and "treated patients" is significant at $.01 < p \leq .05$.

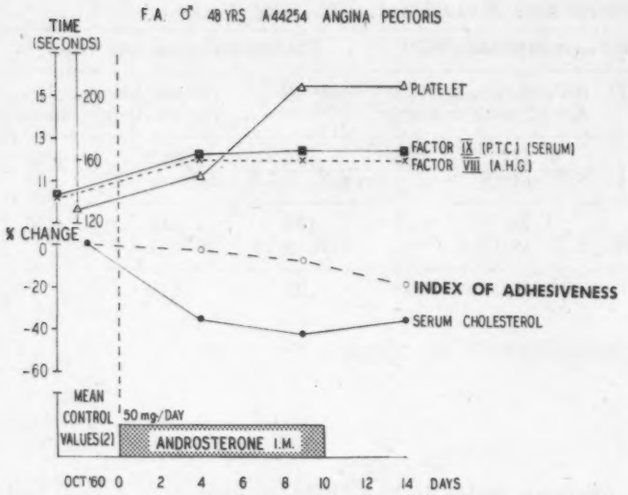

Fig. 4.—Effects of androsterone injected for 10 days at 50 mg./day to a patient suffering from angina pectoris on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

in platelet adhesive index, a prolongation in platelet clumping time, and an increase in thromboplastin generation test, are noted in Table VIII. The results obtained show the same trends as in patients receiving dextro-thyroxine. The changes obtained in a 71-year-old woman with myxedema are shown in Fig. 5. The laboratory findings in this woman were: a B.M.R. of −12; a radioactive iodine^{131} uptake after 24 hours of 4.9%, and a P.B.I. of 2.8 μg. %. The variations in the several tests are more marked than in the euthyroid patient and are shown in detail in Table IX.

TABLE VIII.—PATIENT F.A., A44254, 48 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (3)*
Serum cholesterol	242 mg. %	168 mg. %
Platelet adhesive index	1.52	1.38
Platelet clumping time	127.5 sec.	190 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	10.25 sec.	12 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12.1 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	13.25 sec.	13.5 sec.
(d) Activity of platelets	19 sec.	16 sec.

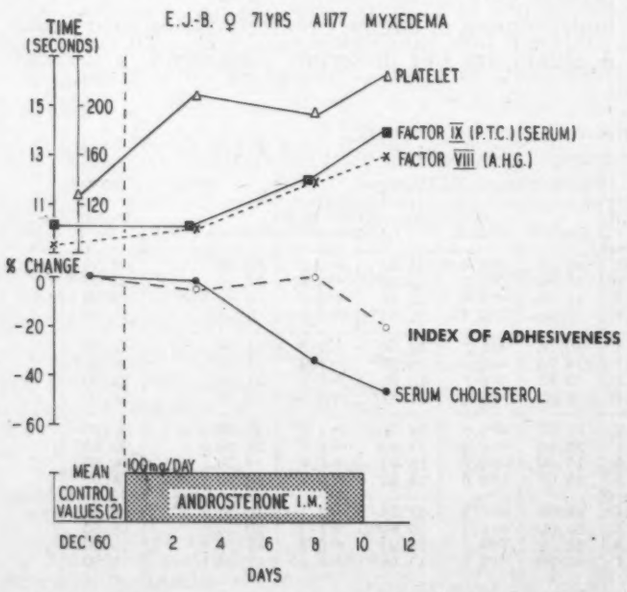

Fig. 5.—Effects of androsterone injected for 10 days at 100 mg./day to a patient with myxedema on the same parameters as in Fig. 1. Note that the legend is the same as that in Fig. 1.

TABLE IX.—PATIENT E.J.B., A1177, 71 YEARS OLD

Tests	*Average control values (2)*	*During treatment mean values (3)*
Serum cholesterol	520 mg. %	346 mg. %
Platelet adhesive index	1.3	1.19
Platelet clumping time	127.5 sec.	210 sec.
At the fourth minute of incubation:		
(a) Activity of aluminum-treated plasma	9.5 sec.	11.5 sec.
(b) Activity of Factor IX (P.T.C.) (measured on serum)	10.25 sec.	12 sec.
(c) Activity of Factor IX (P.T.C.) (measured on plasma)	12.25 sec.	13.5 sec.
(d) Activity of platelets	17 sec.	14.5 sec.

During androsterone administration, one patient developed a nonthrombocytopenic purpura on the fifth day of therapy.

DISCUSSION

These studies demonstrate a direct relationship between the fall in serum cholesterol and changes in factors involved in the first stage of the clotting mechanism during administration of dextro-thyroxine and androsterone to patients with atherosclerosis. The variations in blood coagulation consist of a prolongation of platelet clumping time, a decrease of platelet adhesive index, and an increase in plasma thromboplastin time.

The exact mechanism of this cholesterol-lowering effect is not completely understood, and must be approached on a speculative basis.[1, 23] Dextro-thyroxine has a great advantage over androsterone because it can be given orally, while androsterone must be given intramuscularly only. Dextro-thyroxine causes no side effects, while the site of injection of androsterone in aqueous suspension is very painful.

Our studies established a direct correlation between the atherosclerotic process and thrombotic tendencies which are the major causes of cardiovascular diseases and deaths at the present time. Whether the effects of dextro-thyroxine or androsterone on coagulation are due to the decrease in blood lipids or due to a direct action of the drug *per se* remains to be explained. It would be of great interest to study the changes in the plasma cephalins (phosphatidyl, ethanolamine and phosphatidyl serine) in atherosclerotic subjects receiving dextro-thyroxine or androsterone. Such a study is actually under way in our laboratory.

Androsterone administered intramuscularly definitely has a "thyromimetic" effect on cholesterol level and blood coagulation.

SUMMARY AND CONCLUSIONS

Thirty-one patients were studied; 23 received oral dextro-thyroxine and eight received intramuscular androsterone. The parameters which were investigated showed an over-all decrease of serum cholesterol and platelet adhesive index, a prolongation of platelet clumping time, a decrease in the activity of $Al(OH)_3$-treated plasma and factor IX on serum and plasma, and an acceleration of platelets in the thromboplastin generation test. Three myxedematous patients showed an increase of urinary androsterone and etiocholanolone with dextro-thyroxine therapy. The observed coincidence of the fall of serum cholesterol with the decrease in platelet adhesive index, the prolongation of platelet clumping time, and the increase in plasma thromboplastin time suggests a definite link between lipemia and clotting factors in the pathogenesis of thrombo-atherosclerosis.

We would like to express our deep gratitude to Dr. J. F. Mustard for the invaluable instruction received in his department by two of the authors, C.D. and G.T., and for his help in the preparation of this paper. We wish to thank Dr. Thomas A. Garret of the Baxter Laboratories, for generous gifts of sodium dextro-thyroxine (choloxin); to Syntex, S.A., Mexico, and to Upjohn Company for their generous supply of androsterone. Special mention should be made of the collaboration of Miss Ghislaine Rancourt, medical technologist; Erich Koiw, chemist; Roland Paquette, statistician, Ayerst, McKenna & Harrison Ltd., Montreal; Miss Fernande Salvail, head nurse; Mrs. Anne Brossard, dietitian; and Miss Isabelle Morin, for illustrations.

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CANADIAN JOURNAL OF SURGERY

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The October 1961 issue contains the following original articles, case reports and experimental surgery:

Original Articles: Etude clinique de 238 cas d'endométriose chirurgicale—B. Lambert, P. Meunier et C. Ouimet. The problem of late local recurrence of carcinoma of the cervix—J. P. A. Latour and W. D. Fraser. Hypertensive reaction following resection of coarctation of the aorta—R. K. Padhi, E. M. Nanson and R. B. Lynn. Surgical experience in resection of aneurysms of the thoracic aorta—P. Allen, R. Robertson, W. G. Trapp and W. A. Dodds. Thoracic sequestration cysts of fetal bronchogenic and esophageal origin—G. B. Elliott, G. E. Miller R. H. Walker and K. A. Elliott. Nitrogen mustard in treatment of metastatic carcinoma of the testis—G. J. Ankenman and J. Balfour. Epithélioma colloïde du sein—R. Tremblay et J.-L. Bonenfant. Preauricular sinus—J. A. McLachlin and R. O. Farley. Primary basilar impression of the skull—H. F. W. Pribram and R. J. Porter.

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Experimental Surgery: The etiology and pathogenesis of cholecystitis: an experimental study—D. J. Currie. Some observations on peripheral blood flow, blood gas, and electrolyte content of the dog's limb after sympathectomy—R. K. Padhi and R. B. Lynn. Splenic and bone marrow homografts in the dog after lethal body irradiation—J. W. Irvine and S. Kling.

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CLINICAL STAFF CONFERENCE

PHEOCHROMOCYTOMA

UNIVERSITY HOSPITAL,
SASKATOON, SASK.
MARCH 23, 1961

Moderator:
E. M. NANSON, M.B., Ch.B.(N.Z.), F.R.C.S.(Eng.), F.R.C.S.[C], F.A.C.S.

Discussants:
E. H. BRAUN, M.R.C.S.(Eng.), M.R.C.P.(Edin.), D.T.M. & H.(Liv.)
J. M. CAMPBELL, B.A., M.D., F.A.C.S.
I. M. HILLIARD, B.A., M.D., F.R.C.P.[C]
A. HOFFER, B.S.A., M.Sc., Ph.D., M.D.
Z. F. JAWORSKI, M.D.
C. J. KILDUFF, M.B., B.Ch., F.A.C.A.
E. W. SPENCER, M.D., D.M.R.(Eng.)
C. T. WOLAN, M.D., F.R.C.S.[C]
V. R. WOODFORD, B.S., M.Sc., Ph.D.

Prepared by:
Z. F. JAWORSKI, M.D.

DR. I. M. HILLIARD.* It has been possible to assemble today people from various departments who contributed to the diagnosis or treatment of pheochromocytoma in the patient to be presented. This multidepartmental approach reflects the many facets of this intriguing tumour first described by Fraenkel in 1886.

Considering that only 626 cases had been reported up to January 1957,[1] this tumour is certainly not common. However, it is not to be missed because it is one of the rare, really curable causes of secondary hypertension. These tumours are probably more frequent than the figure just quoted would suggest. I am sure some of us have seen cases which have not been reported, but it is unlikely that anyone has seen enough to have acquired a really valid personal experience with them. Even in large centres more than one dozen cases are seldom seen during many years. The largest series, 51 patients, was reported by Kvale *et al.* from the Mayo Clinic[2] and a series of 36 cases was reported in Scandinavia by von Euler and Ström.[3] The lack of solid personal experience with pheochromocytoma, coupled with its erratic clinical behaviour, results in diagnostic and therapeutic insecurity. This is another reason why we thought it would be interesting to present an apparently typical case which would show the difficulties and pitfalls awaiting the physician and surgeon.

CASE HISTORY

Mrs. O.D. (Hospital No. 66841), a 49-year-old married woman, entered hospital on February 24, 1961, for investigation of hypertension first discovered in August 1960.

Her family history was unremarkable, as was her past history until 1954, the year of her last delivery. Her three pregnancies were uncomplicated. Shortly after, she began to complain of paroxysmal periodic headaches and increasing shortness of breath on exertion, but did not consult her physician. There are no records of her blood pressure level between the time of her last pregnancy and August 1960. At that time, she was admitted to her local hospital because of the sudden onset of right anterior chest and right upper quadrant pain associated with chills, fever, nausea and vomiting. Blood pressure on admission was 260/130-140 mm. Hg. She improved on antibiotics within six days. Her ocular fundi remained normal, but her blood pressure was high (260/140) throughout her stay in hospital.

Investigations at that time showed albuminuria 4+, and 3-5 pus cells and 3-5 red blood cells per high-power field. The blood urea value, initially 60 mg. %, rose to 174 mg. % within three days of her admission and decreased, along with the albuminuria, within three weeks' time. An electrocardiogram (ECG) showed left ventricular strain pattern. A chest radiograph showed an irregular band area in the right base considered to represent pulmonary infarction. A retrograde pyelogram was normal.

After her discharge, her blood pressure was controlled with reserpine and hydrochlorothiazide and maintained at an average of 180/110 mm. Hg. She was re-examined in November 1960 and in January 1961. The sedimentation rate was consistently elevated up to 90 mm. in the first hour. Urine analysis continued to show a few red blood cells in the sediment, but no protein.

The paroxysmal headaches which began after her last pregnancy in 1954 were different in nature from any headaches she had ever had in the past. They were of sudden onset. The severe gripping pain began in the occipital area and neck, spread over the head, and was associated with intense heart pounding. The attacks lasted from thirty minutes to two hours and would sometimes occur just before her menstrual period. Some of the attacks were precipitated by hurrying, emotions, and sometimes by a hot bath, but frequently there was no obvious cause for them; some were followed by intense hunger and thirst. They varied in intensity. She had six or seven particularly severe attacks, one of which was observed in this hospital on March 7, 1961. It occurred suddenly between 8.00 and 9.00 a.m. and was accompanied by profuse sweating, nausea, weakness and anxiety. Her blood pressure was 260/140. She looked pale and shaky. An intravenous injection of 5 mg. phentolamine resulted in a prompt and persistent drop in blood pressure to 125/80.

Since her pneumonia in August 1960, she had tended to sweat profusely, sometimes continuously for several hours. This required at times a change of pyjamas twice a night. The sweating was not necessarily associated with headaches.

Between attacks, she felt relatively well apart from being tense, nervous and short of breath on exertion. Her appetite remained good. There was a loss in weight of approximately 10 lb. over five years. She had no visual complaints. She had no chest pain, nocturnal

*Professor and Head of Department of Medicine.

dyspnea or nocturia. She tended to be dizzy on getting up quickly from bed or on changing position. She tolerated heat poorly.

Physical examination disclosed a thin, tense woman weighing 98½ lb. Blood pressure on the first examination was 274/132-140 mm. Hg in both arms in the prone position. Pulse was 82 per minute and regular. She had no pyrexia. Fundi showed well-delineated discs with the central vein pulsating. There was an increase in light reflex of the arteries, marked segmental narrowing and moderate arteriovenous (A-V) nicking. A harsh grade three systolic precordial murmur was transmitted to the neck and axilla and was maximal in the left parasternal area. There was a diffuse left ventricular heave. The left heart border was located in the fifth intercostal space close to the anterior axillary line. The second aortic sound was markedly accentuated. Peripheral pulses were felt in all areas. On examination of the abdomen, there was slight guarding in the right epigastric area, and a mass, which could have been the kidney, was palpated in the right flank.

After admission, the patient was taken off all medication, for investigative purposes. Blood pressure in the prone position varied greatly, ranging from 270-170 systolic/130-110 diastolic. On standing, there was often a drop in blood pressure to as low as 140/95.

Results of Tests and Investigations

Hb. 12 g., P.C.V. 39%, R.B.C. 4,300,000, W.B.C. 4100 with a normal differential, and E.S.R. 91 mm. in the first hour. Serum proteins—total 6.7 g./100 ml. (albumin 3.4, total globulins 3.2; gamma globulin 1.3 g./100 ml.).

On urine analysis, the specific gravity in random specimens ranged from 1.015 to 1.020 and maximal specific gravity was 1.022. There was no proteinuria except during an attack of hypertension. In the urinary sediment occasional red cells and white blood cells were found. Urine culture was negative. B.U.N. was 21 mg./100 ml. Serum electrolytes were within normal limits.

B.M.R. was +21 and +29, and blood cholesterol 255 mg./100 ml. Protein-bound iodine was 5.5 μg. per 100 ml. Radioactive iodine uptake showed a low normal value of 12%.

Glucose tolerance curve was normal. Fasting blood levels ranged from 108 to 110 mg. per 100 ml.; the peak was at one hour at 165; the two-hour value was 112 and three-hour value 106 mg. per 100 ml. There was no glycosuria. During the attack of hypertension, blood sugar was 168-155 mg. per 100 ml.

TABLE I.—EXCRETION OF 3-METHOXY-4-HYDROXYMANDELIC ACID (VMA) AND R VALUES*

Mrs. O.D., Hospital No. 66841.

	R. values†		*VMA (μg./mg. creatinine)*	
	Mean	*Range*	*Mean*	*Range*
Normal subjects	2.09	1.58-2.26	1.6	0.7- 2.5
Essential hypertension	1.82	1.42-2.25	1.5	0.5- 4.0
Pheochromocytoma	0.74	0.45-1.16	16.0	7.5-30.0
Patient, Mrs. O.D.				
Preoperative, March 1961		0.71-0.92		
Postoperative, April 7/61		1.82		

*According to Gitlow *et al.*[4].

†The optical density of the final tested sample is determined spectrophotometrically at wave length 450 mμ and 550 mμ. The ratio (R) of Density 450 and 550 is related to the content of VMA in the sample as the Density 550 increases with VMA concentration. For details consult original paper.[4]

TABLE II.—CATECHOLAMINE EXCRETION (μg. per 24 hours)

Mrs. O.D., Hospital No. 66841.

Days before operation	*NA*	*A*	*Total*
13	232	130	362
12	271	199	470
11	298	203	501
10	714	145	859
Days after operation			
2	120	41	161
3	86	30	116
4	57	24	81

Phentolamine (Rogitine) tests were repeatedly consistent with pheochromocytoma. A histamine test was strongly positive. Base-line blood pressure was 180/115. Although only 0.0125 mg. of histamine base was injected intravenously (one-quarter of the recommended dose), there was a rise of systolic blood pressure within 30 seconds to at least 300 and 170 mm. Hg diastolic, and all manifestations of her spontaneous attacks were reproduced. Two injections of 5 mg. phentolamine were required to bring the attack under control. Urinary 3-methoxy-4-hydroxymandelic acid (Table I) and the 24-hr. output of catecholamines (Table II) were elevated.

ECG showed sinus rhythm, a rate of 70 per minute, left ventricular hypertrophy and strain.

Chest x-ray showed a moderate degree of left ventricular enlargement. Intravenous pyelography showed prompt excretion of the dye in good concentration. Retroperitoneal gas insufflation was suggestive of a nodule in the left adrenal area (Figs. 1 and 2).

Course in Hospital

On March 7, 1961, she had a major hypertensive attack as described. On March 11 and March 27, she had lesser attacks, during which her blood pressure was 280-270/150.

On March 15, the patient underwent an exploratory operation of the left retroperitoneal space; no tumour was found and the left adrenal, which was removed, was normal. She remained hypertensive.

On April 6, a laparotomy was performed and a chromaffin tumour located between the duodenum and the lower pole of the kidney was removed. The right adrenal gland was normal.

Postoperative Condition

Following the second operation, her blood pressure fell initially to 140 systolic/90 diastolic and stabilized at 155-160 systolic/90 diastolic in the prone position. On standing, it was 140 systolic/88 diastolic. She felt more relaxed and ceased to perspire. Physical examination 12 days after operation showed no changes in the funduscopic examination. The precordium appeared quieter, but cardiac findings were otherwise unchanged. On electrocardiogram, considerably lower voltages in the left precordial leads were noted and there was some regression of ST-T changes.

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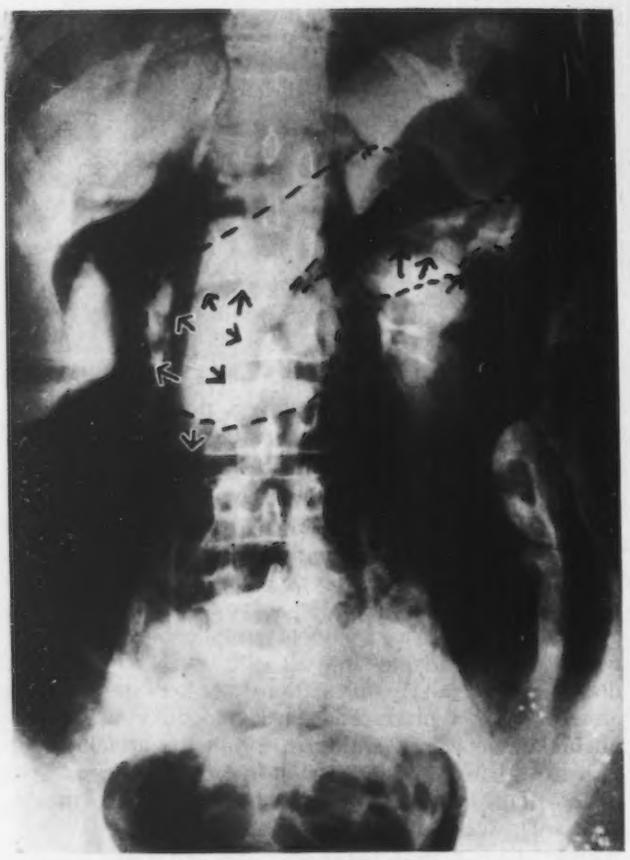

Fig. 1.—Mrs. O.D., Hosp. No. 66841. Intravenous pyelogram and retroperitoneal presacral carbon-dioxide (CO_2) insufflation, March 8, 1961. Fifteen-minute I.V.P. following presacral retroperitoneal CO_2 insufflation showing outline of spleen lying in peculiar transverse position (dotted line), fitting on to and depressing the upper pole of the left kidney (see arrows). The pancreas is also outlined by the dotted line showing the tail displaced upwards and overlying the well-outlined left adrenal. Arrows on the right side of L2-L4 outline a second density which was later recognized as the tumour.

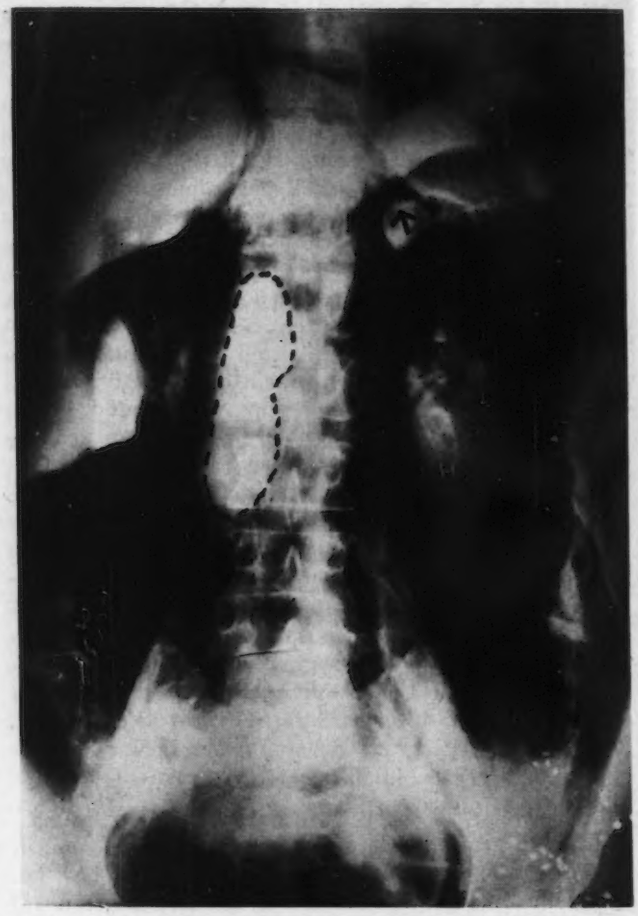

Fig. 2.—Mrs. O.D., Hosp. No. 66841. Intravenous pyelogram and retroperitoneal presacral carbon-dioxide (CO_2) insufflation, March 8, 1961. Denser film of combined retroperitoneal CO_2 and I.V.P. shows persistent outline of "adrenal medulla" within the surrounding adrenal cortex. The dotted outline with more penetration on the film outlines the tumour but not the pancreas or spleen. **Note:** This "adrenal medullary configuration" was consistently reproduced on the majority of films but was, in fact, an adenoma in the tail of the pancreas ectopically and accurately overlying the left adrenal.

DR. E. M. NANSON.* We shall start with the diagnostic problems first. Dr. Spencer, would you please show us the films now?

DR. E. W. SPENCER.† Chest film shows a moderate degree of left ventricular enlargement. The chest is otherwise normal in appearance.

Intravenous pyelograms are normal. However, it is noted that the left kidney is slightly lower than the right.

Intravenous pyelogram and presacral and perirenal air insufflation (Figs. 1 and 2) show nothing abnormal on the right side. The left suprarenal is identified. It measures 3 cm. in diameter and is considered to be somewhat large. Overlying the left suprarenal, and contained within its periphery, there is a rounded area of increased density. This has the appearance of a nodule within the suprarenal. Lying opposite the body of the second lumbar, and projecting to the right of the midline, there is a somewhat lobulated area of increased density, measuring 9 x 4 cm., which has the appearance of a mass of soft tissue. Its nature was not clear. It could represent extension of the tumour, accessory spleen or possibly the pancreas.

*Professor and Head of Department of Surgery.
†Professor and Head of Department of Diagnostic Radiology.

DR. NANSON. I am sure Dr. Wolan would like to review the x-ray findings later. Dr. Jaworski, would you care to comment on the problem of clinical diagnosis in this patient?

DR. Z. F. JAWORSKI.* Although we failed to localize the tumour correctly, the diagnosis of pheochromocytoma in this patient was not difficult. Her hypertension was more or less sustained, as is the case in two-thirds of these tumours, but, in addition, she had typical attacks of paroxysmal hypertension. She also manifested excessive sweating, postural hypotension and tachycardia, hypermetabolism without thyrotoxicosis, loss of weight, hyperglycemia during the attacks, and marked nervousness. The presence of several of these manifestations in one patient should arouse one's suspicion as to the possibility of chromaffin tumour.

A few further observations on our patient deserve brief comment. It has been noted previously that a febrile illness in a patient harbouring a chromaffin tumour may induce a severe and continuous rise in blood pressure. In our patient, the

*Lecturer in Medicine.

febrile illness revealed the severity and curious nature of her hypertension. She also showed intermittent albuminuria and a persistently elevated sedimentation rate in the neighbourhood of 90 mm. in the first hour, which promptly fell to normal after the successful operation. Of course, continuous albuminuria is seen in hypertensive cardiovascular disease, and elevation of the sedimentation rate does occur in accelerated and malignant phases of hypertension, but not in uncomplicated essential hypertension. It is uncertain how consistently or specifically intermittent albuminuria and elevation of sedimentation rate occur in cases of pheochromocytoma, although reference to "paroxysmal nephritis" was made in some cases.[18] It is interesting to note in this regard that infusion of catecholamines may result in transient albuminuria.[19] Both these manifestations then are worth remembering.

On physical examination, the discovery of an abdominal mass in a hypertensive patient is of great importance because, if massaging of the mass reproduces a typical attack, the diagnosis is made and the tumour is located for the surgeon. We felt the abdominal mass in our patient but, because no attack occurred on palpation, we considered the mass to be the right kidney in view of its location. The radiological findings suggested that the tumour was located in the area of the left adrenal and thus further diverted our attention from the mass. Probably because of the use of phenoxybenzamine hydrochloride with its blocking action of the catecholamines, the mass and its nature escaped detection when palpated during the first operation.

In the past, many patients would have been explored surgically on the basis of our patient's history and physical findings. If the manifestations of pheochromocytoma are less clear-cut, the diagnosis is further corroborated by either provocative or blocking tests. The results of phentolamine (Rogitine) and histamine tests were unequivocally positive in this patient. However, these tests are indirect and are liable to show both false negative and positive results. The phentolamine test is notorious for giving false positive results in patients who have been given sedatives or tranquillizers, and also in those with renal insufficiency. The histamine test is not without danger, since vascular accidents may occur during the induced hypertensive attack. In our patient, two intravenous injections of 5 mg. phentolamine had to be used at two-minute intervals to bring the resultant severe rise in blood pressure under control.

Recently, Gitlow *et al.*[4] devised a simple colorimetric test for pheochromocytoma based on a semiquantitative estimation in the urine of a final metabolite of catecholamines, 3-methoxy-4-hydroxymandelic acid.[4] Prior to our patient's operation, the result of this test was consistent with the diagnosis of pheochromocytoma (Table I). Twenty-four hours after operation, the test result became negative. If this test continues to give consistent results and, in particular, no false negative results, it may replace the indirect blocking tests and possibly the provocative tests as a screening procedure. The final proof of the existence of chromaffin tumour in a given case must be made, if necessary, by urinary catecholamines estimation.

DR. J. M. CAMPBELL.* This case shows how varied the mode of presentation of these tumours may be and exemplifies various precipitating causes of the acute attack. A rather interesting and curious example of pressure on these tumours is seen when they are present in the bladder wall. There have been ten cases of pheochromocytoma of the bladder reported.[5] In some of these, the acute symptoms are precipitated by voiding. In these circumstances, micturition brings on an attack of weakness, a pounding headache, palpitation and an immediate elevation in blood pressure.

DR. JAWORSKI. Along this line, one should mention that apart from the association of pheochromocytoma with false diabetes, other combinations were noted. There have been 13 cases of pheochromocytoma reported in association with pregnancy, some manifested as pre-eclampsia.[6] Pheochromocytoma is found in a greater proportion of patients with neurofibromatosis than one would expect in the general population. Finally, cases of familial incidence of pheochromocytoma have been reported; in these, the tumour may develop and give rise to symptoms in infants and children.[7]

DR. NANSON. Dr. Woodford, would you please discuss for us the significance of catecholamines in the diagnosis of pheochromocytoma.

DR. V. R. WOODFORD.† The end-products of catecholamine catabolism found in the urine are adrenaline and noradrenaline as such, their sulfate or glucuronide conjugates, their 3-methoxy derivatives and 3-methoxy-4-hydroxymandelic acid, as well as 3,4-dihydroxymandelic acid. The catabolism of the catecholamines has been ably summarized by Axelrod.[8]

Many methods have been devised for the estimation of the catecholamines and their derivatives. Some of these measure both noradrenaline and adrenaline excretion while others measure the excretion of a common end-product of metabolism; for example, the measurement of 3-methoxy-4-hydroxymandelic acid does not distinguish between adrenaline or noradrenaline metabolism. The method in use in our laboratory for the estimation of the urinary excretion of adrenaline and noradrenaline is that of Drujan *et al.*[9] Mean normal values obtained by these authors are about 16 μg./24 hr. for adrenaline and 55 μg./24 hr. for noradrenaline. Normal ranges were: adrenaline 3-31 μg./24 hr., and noradrenaline 25-130 μg./24 hr.

The results of the estimations for urinary catecholamines for Mrs. O.D. are presented in Table

*Assistant Clinical Professor of Surgery (Urology).
†Assistant Professor of Biochemistry.

II. These results show that the excretion of both noradrenaline and adrenaline were higher than normal. The value obtained for noradrenaline on the tenth day before operation is of special interest. On this day, the patient had a hypertensive attack which was accompanied by an increased noradrenaline excretion amounting to more than twice as much as that excreted on any of the previous three days.

Postoperatively the catecholamine excretion was diminished (Table II). A steady fall in the output of both adrenaline and noradrenaline occurred during the second, third and fourth postoperative days to values within the normal range.*

It is interesting to speculate that the steady fall in catecholamine excretion during the three postoperative days investigated represents a slow release of these substances from extra-tumour storage sites.

The adrenaline formed in the body is formed almost entirely in the adrenal medulla, where the adrenaline to noradrenaline ratio is approximately 5:1. Noradrenaline is produced at the effector endings of the adrenergic nerves and, in the fetus, by the organ of Zuckerkandl. In the overall excretion of catecholamines from the body, the proportion of urinary noradrenaline is much greater under normal conditions than that of adrenaline. There is thus a theoretical basis for the suggestion by von Euler[10] that analyses of urinary adrenaline and noradrenaline might reveal whether the pheochromocytoma is of adrenal medullary origin or is of extra-adrenal origin.

Crout and Sjoerdsma[11] have presented evidence to show that if the adrenaline excretion is elevated, the site of the tumour is most likely to be in either the adrenal gland itself or the abdomen close by. If only the noradrenaline excretion is elevated, the site of the tumour may be anywhere in the body. If these relationships hold, then the differential estimation of adrenaline and noradrenaline may be of some assistance to the surgeon in locating the site of the tumour.

Analysis of the tumour after removal from the patient revealed the catecholamine concentrations which are presented in Table III. These values fit into the range reported in the literature.[12]

TABLE III.—CATECHOLAMINE CONTENT OF THE TUMOUR

Mrs. O.D., Hospital No. 66841.

	Adrenaline	*Noradrenaline*	*DOPAmine*	*Total CA*
µg. per mg. (wet weight)	0.14	3.42	0.16	3.72
mg. in tumour (tumour weight =72 g.)	10	246	12	268

*Analyses for adrenaline and noradrenaline carried out on days 48 and 49 postoperatively gave values equivalent to those of the fourth postoperative day, indicating that by this time the catecholamine excretion had returned to its characteristic level.

DR. NANSON. The problem in regard to this patient was that she had had an exploration of her left adrenal area where the pheochromocytoma was thought to be located. This had been carried out by Dr. C. T. Wolan and no obvious tumour had been found in the left adrenal area. At the time of the left adrenal exploration, which was carried out through a left kidney incision, the peritoneum was opened and Dr. Wolan had explored the rest of the abdomen as well as he could through this incision. He did not locate the tumour, however.

After this first exploration, repeated biochemical studies showed that this person must have a pheochromocytoma. There was no indication that this tumour existed above the diaphragm. Chest radiographs were entirely normal. There was no lesion to be found in the neck. Therefore, it was likely that the tumour was in the abdominal cavity. The differential urinary catecholamine determination strongly supported this view. The possible locations where it might be found were in the right adrenal area, in the paraganglionic area related to the sympathetic chain, or in the area of the organs of Zuckerkandl.

It was therefore decided that this patient must have a laparotomy. Accordingly, this was carried out on April 6. After anesthesia had been induced, an indwelling intra-arterial needle was placed in the right femoral artery and connected to a transducer which gave us a continuous blood pressure record both on a recording photographic chart and also on an oscilloscope. At this stage, the patient was purposely not blocked with any ganglionic blocking agent.

The abdomen was opened through a right midparamedian incision and exploration was carried out. Firstly, the left adrenal area was re-explored and no abnormality was found there. The right adrenal area was also explored and no abnormality was found there. Then, on exploring along the right side of the vertebral column, it was evident that there was quite a large tumour situated in front of the inferior vena cava and behind the second and third parts of the duodenum. This was a tumour of about 5 cm. in length by 2-3 cm. in width. It was moderately firm. On palpation of this tumour, an immediate rise in the blood pressure occurred, indicating that we were dealing with a functional pheochromocytoma. The duodenum was therefore carefully reflected off the front of the tumour by incising the peritoneum along its lateral aspect and the dissection of the tumour was carried out. This was done very gently. It was found that two veins were passing from the tumour into the anterior surface of the inferior vena cava. These were clamped and divided. As soon as we began to manipulate the tumour in its dissection, the blood pressure began to rise and therefore the anesthetist, Dr. J. C. Kilduff, controlled this rise with intravenous injections of Rogitine. When we came to the dissection around the draining veins which went into the front of

the inferior vena cava, the blood pressure rose quite considerably to 300 mm. Hg, and further injections of phentolamine (Rogitine) were required. The tumour was removed without difficulty and slowly over the next five to ten minutes the blood pressure fell quite considerably. At this stage, a noradrenaline drip was set up to maintain the pressure at a satisfactory level. The abdomen was closed in a routine manner. Following the operation, the patient had an uninterrupted convalescence.

DR. NANSON. Dr. Braun, what was the tumour like histologically?

DR. E. H. BRAUN.* The specimen consisted of a pinkish-grey, well-encapsulated mass, weighing 74 g. and measuring 10.5 x 4.8 x 27 cm. Histologically, it is a well-differentiated and benign-looking pheochromocytoma. Sections fixed in chromate solution revealed typical minute, brown, cytoplasmic granules.

DR. NANSON. Dr. Kilduff, the choice and conduct of anesthesia were important to the surgeon. Would you care to comment on this?

DR. C. J. KILDUFF.† This patient was presented for anesthesia and surgery first with the diagnosis of pheochromocytoma in the left adrenal area.

After consultation with Professor Mark Nickerson, it was decided to give phenoxybenzamine HCl (Dibenzyline HCl) intravenously to the patient. Dibenzyline HCl is highly effective in the specific blockade of excitatory responses to adrenergic stimuli. It has also been used to prevent cardiac arrhythmias.

The day before the operation this patient was given 1 mg. Dibenzyline/kg. body weight intravenously. Blood pressure before the administration was 210/120 mm. Hg and pulse rate 84 per minute. After 90 minutes, the blood pressure was 80/60 mm. Hg, during which time 25 mg. of Dibenzyline was given. The intravenous infusion was stopped for 15 minutes, whereupon the blood pressure rose to 120/80 mm. Hg after bandaging of the legs and placing the patient flat. The remainder of the drug was given during the next fifteen minutes without any changes in blood pressure, which also remained stable during the night.

The next morning the same dose of Dibenzyline was given 90 minutes before induction of anesthesia, without any further change in blood pressure. Endotracheal anesthesia was maintained with sodium thiopental, nitrous oxide–oxygen and an azeotropic mixture of halothane and ether with d-methyl-tubocurarine added for relaxation. Respirations were controlled during surgery.

Blood pressure dropped momentarily when the periosteum was being stripped from the left twelfth rib and during exploration of the abdomen with the patient in the acutely flexed kidney position.

The tumour was not found during this operation. After three hours of anesthesia, blood pressure had risen to 160/100 mm. Hg and reached 200/120 mm. Hg in 10 minutes, having averaged 120/80 mm. Hg during the operation.

Dibenzyline was not used during the second operation, as there was now some doubt as to the exact location of the tumour. It was decided to control blood pressure with phentolamine and noradrenaline.

General anesthesia was conducted in the same fashion as during the first anesthetic.

Before anesthesia, blood pressure was 220/120 mm. Hg and fell to 125/90 mm. Hg after induction and remained so until the peritoneum was opened. The tumour was located and, on manipulation of the tumour, the blood pressure rose to 270/120 mm. Hg with a bout of cardiac arrhythmias. Manipulation was stopped temporarily and the blood pressure and arrhythmias were controlled with 5 mg. phentolamine intravenously. This dose was repeated on another five occasions to control the blood pressure; cardiac arrhythmias were infrequent after the first occasion.

On removal of the tumour, the blood pressure immediately fell from 270/130 mm. Hg to 110/90 mm. Hg and then to 80/60 mm. Hg over the next 15 minutes. Noradrenaline administration was delayed for five minutes after removal of the tumour to eliminate the possibility of a second tumour. It was then begun as an intravenous drip. Twenty minutes after noradrenaline was started, the blood pressure started to rise and reached 120/80 mm. Hg in 10 minutes, at which time the operation was finished.

The patient remained for 45 minutes on the operating table to stabilize. One hour later she was fully awake in the recovery room.

Blood pressure maintained itself at approximately 120/80 mm. Hg. Noradrenaline was discontinued after four hours and 45 minutes without any change in blood pressure.

The total dose of noradrenaline used was 0.04 mg.

This was a very interesting case as it gave a very rare opportunity to use two different techniques to control blood pressure in the same patient within a short period of time. It also demonstrated that manipulation of the tumour, although not recognized at the time owing to the type of incision in the first operation, did not alter blood pressure or produce cardiac irregularities when the patient was blocked with Dibenzyline. The unblocked patient during the second operation demonstrated the hazards of the phentolamine method.

Cardiac arrhythmias are not uncommon during anesthesia and their incidence is increased by a high level of catecholamines. The hypertensive crises can give rise to acute pulmonary edema or cerebral hemorrhage. Prolonged use of noradrenaline intravenously can lead to local damage of the

*Assistant Professor of Pathology.
†Assistant Professor of Anesthesia.

limb and produce a ganglionic type of blockade which makes the patient very dependent upon noradrenaline.

The use of phenoxybenzamine with an exploratory laparotomy would appear to make the anesthesia and surgery safer for the patient. It does make the localization of a very small tumour and secondary tumours more difficult. Small tumours are more likely to produce a lower level of catecholamines than this large tumour and make the use of either technique safer.

DR. NANSON. Dr. Wolan, do you agree with Dr. Kilduff's statement that use of phenoxybenzamine with an exploratory laparotomy does not make the surgeon's task more difficult in finding or identifying the tumour?

DR. C. T. WOLAN.* In hindsight, if we had not been so certain that the left adrenal contained the tumour and attacked it directly as we did, maybe it would not have been advisable to "block" the patient preoperatively because certainly during the four palpations of the "duodenum" she would have become hypertensive and given us a clue. This is particularly true with the femoral catheter and pressure recording hook-up that we used for the second operation.

DR. NANSON. Dr. Wolan, what do you think of retroperitoneal air as a diagnostic tool in localizing pheochromocytoma?

DR. WOLAN. In this particular case it was misleading and we did not interpret the findings properly. Since the majority of these tumours occur in the adrenal, if the adrenal can be adequately visualized with retroperitoneal air insufflation it certainly is a good clue to the diagnosis. Presacral retroperitoneal carbon dioxide insufflation is a relatively safe and good procedure.

DR. NANSON. Would you care to say a few words about this particular case, Dr. Wolan?

DR. WOLAN. Hindsight is a wonderful thing. It has taught us several lessons. When I palpated intra-abdominally through a rent in the peritoneum from the left flank, I could not feel any masses or nodules along the course of the right sympathetic chain. The whole left sympathetic was previously visualized retroperitoneally. Nothing palpable was felt in the region of the right adrenal, with the kidney feeling normal as well. We identified what we thought to be the second part of the duodenum, retroperitoneally, on four separate palpations and thought out loud, "This is the duodenum. This is the right kidney and it feels normal. Here should be the adrenal and it cannot be felt. There certainly is no fullness or nodularity here." We also felt the preaortic and the subaortic areas within the pelvis. The whole right sympathetic chain area was also palpated and nothing was found.

May we have the second films shown, Dr. Spencer?

*Clinical Teacher in Urology.

There is a little too much CO_2 in these films (Figs. 1 and 2) because, for some reason, it did not absorb as quickly as it often does. See this rounded mass here, lateral to the body of the third lumbar vertebra? In our conference prior to the second operation, I said that this rounded figure bothered me and asked Dr. Nanson if it was the duodenum end where the second part meets the third. Dr. Nanson replied that he had never seen the duodenum with retroperitoneal air studies and could not say. After having viewed the tumour behind the second portion of the duodenum, between it and the vena cava, we can see that it exactly fits the location and outline of the tumour. Here is what we so definitely thought was the tumour in the medulla of the adrenal. It is consistent on all the films. This, in retrospect, is the adenoma in the tail of the pancreas which we biopsied. It is fixed in this area, with the tail of the pancreas being much more superior than is usual. Here is the rest of the pancreas and here is the tumour. The adenoma of the tail of the pancreas superimposed on the adrenal so regularly and persistently was a "red herring".

We also wondered about this rounded mass below the bifurcation of the aorta in front of the upper portion of the sacrum. This undoubtedly is sigmoid on end, but that is why we asked Dr. A. B. Brown to see her and do a pelvic examination to see if he could feel something above the uterus. The pelvic examination was reported as negative. We have all, and I in particular, learned a good lesson from this case.

DR. NANSON. I think there are one or two important points to be made in connection with the surgery of a patient suspected of having a pheochromocytoma. I feel rather strongly that the difficulty of accurate localization of the tumour is such that these patients should always be explored by means of a laparotomy. It is very important to be able to explore all the possible areas where a pheochromocytoma might exist, namely, both adrenal areas where some 90% of the tumours will be found, together with the para-aortic areas along the sympathetic chains and the area of the organs of Zuckerkandl below the bifurcation of the aorta. The second point of importance is, I think, the virtue of monitoring the blood pressure continually by means of an indwelling intra-arterial needle. If there is any doubt about a tumour, the palpation of the suspected area may demonstrate a sharp rise of blood pressure, which is highly significant in so far as it indicates that the area that is being palpated is the seat of a tumour which is producing a vasopressor. I think it is unwise to block these patients in advance before the exploration has been carried out, as you may prevent elicitation of this useful sign of a rise of blood pressure associated with palpation of the tumour. The third point is that, having removed the tumour, it is important to explore the other areas where tumours may be found, as occasionally these

tumours are multiple. Fourthly, during the removal of the tumour, manipulation should be as gentle as possible, and if there is a rise of pressure at this time, the anesthetist should block the effect of the catecholamines so released by means of Rogitine. This worked very well in this tumour and at no time gave us undue concern. The fifth point is that when the tumour is removed there may be a fall of pressure to a degree that a vasopressor is required and noradrenaline is the ideal drug for this and a noradrenaline drip should be maintained to produce an adequate blood pressure until such time as it is no longer required.

It is important in exploring the abdomen to make sure that there are two normal adrenal glands. Occasionally one may be absent or atrophic and, if the tumour is located in the good adrenal gland, then the removal of this may precipitate the patient into an adrenal deficiency state.

One of the striking features in the postoperative state of this particular patient was the feeling of well-being that resulted once the tumour was removed, with the decrease in the symptoms of nervous tension which she had before the operation.

Dr. Hoffer, you saw this lady. Have you any comments on the emotional reactions to catecholamine excess?

DR. A. HOFFER.* The relationship of adrenaline to mood is a very interesting one. Surgeons are especially interested in the connection between adrenaline and pheochromocytoma. Internists are interested in its relationship to blood pressure. Psychiatrists are interested in the possible connection between mood and adrenaline.

We in psychiatry have tended to look upon depression as primary, that is, as a cause which would elevate adrenaline levels. This case, however, illustrates that the increased secretion of adrenaline can be a cause of irritability and depression. There are many cases in the literature where this has indeed been the case and many of us in the field of psychiatry are now becoming concerned about determining which really is cause and which is effect.

This patient was clearly tense, irritable and depressed. I gave her an HOD test.[13] I have given this test to a large series of patients. From the test it is possible to arrive at a depression score. The mean score for a hundred normals was 0.87 with only four normals scoring 4 or more and the highest score being 5. The mean of one hundred patients examined in a random series was 7.76. Only ten scored between 0 and 3, and 90 scored over 4. This difference, of course, is highly significant. This patient was given the test and it was asked that she complete it on the basis of her feeling for the month before her operation. She had a depressive score of 7. It was, of course, quite obvious from her history even without this simple test that she had been quite irritable and depressed. A couple of days later, after the operation, she was asked to do the test on the basis of her feeling since the operation and this time her depression score was zero.

It is therefore likely that this patient was depressed owing to her excessive secretion of adrenaline and also because of her feeling that perhaps the physicians would not be able to find the cause of her problem and therefore would be unable to treat it.

I was especially interested in the very high levels of sympathomimetic amines found in the urine. It is well known that only about 1% to 4% of these compounds when given by vein appear free in the urine, so that one can logically give a correction factor of perhaps 50-100. If one does this, it is quite obvious that she was secreting many milligrams per day. The question is—how was she able to tolerate so much? With animals, one can give increasing quantities of adrenaline to which the animal adapts and perhaps this is what happened in this case.

Dr. Manger used serum levels of adrenaline-like substances.[14] At the Mayo Research Foundation they suggest that 6.8 μg. per litre indicates pheochromocytoma. With essential hypertension, the range is 1.5-1.8, whereas with normal people it is much less.

This case, therefore, is another example of the inter-relationship of certain chemical hormones to mood.

DR. NANSON. Dr. Jaworski, how successful have we been in curing this lady?

DR. JAWORSKI. There are two aspects to be considered in the prognosis for a case of pheochromocytoma. Firstly, occasionally there is the problem of recurrence of tumour and hypertension after a variable period of time following successful surgery. The question then arises as to whether one is dealing with the development of a new tumour or the metastasis from the original tumour. Only 10% of pheochromocytomas are malignant, but both histologically and clinically it may be difficult to decide whether one is malignant or benign. Both types may infiltrate locally and grow in blood vessels. The fact that a tumour is well encapsulated does not guarantee that it will not metastasize. A case reported in Canadian literature by Belkin, McQueen and Duffin[15, 16] bears out this fact. On the other hand, there are reports of recurrences of hypertension due to the development of another chromaffin tumour *de novo*.[17] On a statistical basis, the chances are good that our patient's pheochromocytoma was benign and will not recur.

Secondly, the prognosis in these cases will depend on the effect of the removal of the pheochromocytoma on the blood pressure. In many instances removal of the tumour or, for that matter, removal of any specific cause of hypertension, may not result in return of the blood pressure to normal.

*Associate Professor (Research) of Psychiatry.

The left ventricle, the arteries and the arterioles, and hence the perfusion and the health of the myocardium, the cerebral and renal parenchyma, all may have been compromised by the hypertension due to a specific cause and these changes, including hypertension, may become irreversible. Some think that irreversible hypertension in these instances is due to secondary renal involvement. In our patient, renal function was grossly normal but there were definite hypertensive retinal changes, and left ventricular hypertrophy, and her blood pressure following operation did not return to normal although it was greatly diminished. It is suggested that false negative Rogitine tests in some cases of pheochromocytoma may be due to the fact that irreversible hypertension is already established. Considering that hypertension of any cause may become irreversible, one should attack the remedial and specific causes without undue delay. We do not know at the present time what course the hypertensive cardiovascular disease will take in our patient.

DR. NANSON. Thank you, gentlemen, for your attention. Our time is up, but I think you will agree that this patient with pheochromocytoma has served a most useful purpose. She has been the means of synthesizing the departments of medicine, surgery, anesthesia, biochemistry, pathology, psychiatry and radiology over a common problem. In our turn, I hope we have helped her.

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REVIEW ARTICLE

RECTAL BLEEDING IN INFANCY AND CHILDHOOD*

ROBERT A. MACBETH, M.D., F.R.C.S.[C],†
Edmonton, Alta.

FEW SYMPTOMS cause a mother to seek medical attention for her child with greater dispatch than does that of the appearance of fresh or altered blood associated with the stool. This is indeed fortunate for, while the cause may be inconsequential, this symptom may herald the presence of serious disease requiring urgent therapy and even emergency surgery.

The recent occurrence of three instances of severe bleeding from the rectum in children in my practice has prompted me to examine the records of such cases in this area and survey the rather meager literature on the subject. It soon became apparent that the standard coding of discharge diagnoses of hospitalized patients did not make it possible for record librarians to provide charts of patients on a basis of their presenting complaint with any consistency. In response to a request for the records of all patients under the age of 16 with rectal bleeding or melena in two Edmonton hospitals only 63 charts were made available. None of the personal cases were included in the records provided because they were discharged as Meckel's diverticulum, thrombocytopenic purpura and gastrointestinal angiomatosis. A complete review of local experience was therefore virtually impossible. The excellent classification of Koop[7] has consequently been selected as the background against which selected cases will be discussed in an attempt to clarify the differential diagnosis and treatment of rectal bleeding in infancy and childhood.

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†Department of Surgery, University of Alberta, Edmonton.

SYMPTOMATOLOGY

There is rather universal agreement that a carefully elicited history is frequently the most valuable part of the evaluation of any case of rectal bleeding. The following points must be established, if at all possible.

1. *How Much Blood Has Been Passed?*

This information may help with the diagnosis but is even more important in the assessment of the urgency of the situation. It must constantly be kept in mind that the loss of a quantity of blood which in the adult would be inconsequential may

well constitute a massive hemorrhage in a small infant. The loss of 40 c.c. of blood by a 6-lb. newborn, for example, is roughly equivalent, on a basis of its effect on circulating blood volume, to a hemorrhage of 1000 c.c. in a 150-lb. adult.

2. *How Long Has the Patient Been Bleeding?*

This information, like that of the amount of blood passed, is usually more helpful in assessing the gravity of the situation than in establishing the precise diagnosis.

3. *What Colour is the Blood?*

The colour of the blood passed depends on three factors: (i) The proximity of the source of bleeding to the anal orifice. (ii) The rapidity with which it is conveyed from the source of bleeding to the anal orifice. (iii) Whether it has been in contact with acid secretions which give it a brownish colour as a result of the formation of acid hematin.

It is not an uncommon error to fail to consider these latter two considerations, for while it is true that bright red bleeding usually indicates an anorectal or at least a colonic lesion, large quantities of blood in the small intestine may be transmitted along the bowel rapidly enough that it presents at the anus as bright red in colour.

4. *Is the Blood Mixed With the Stool or Only on the Surface?*

Bleeding into the small bowel or colon above the sigmoid is usually intimately mixed with the stool owing to the action of intestinal peristalsis on the liquid or semi-solid feces. We have been surprised on reviewing charts to note how often this information is missing, either because the question was not asked or more commonly because the informant was unable to answer it.

5. *What is the Relationship of the Passage of Blood to the Passage of Stool?*

The significance of this can be best appreciated when specific disease entities are considered.

6. *Are There Any Associated Symptoms?*

The presence or absence of associated symptoms and their nature is probably the most helpful information in the establishment of a precise diagnosis. The presence of abdominal or anal pain, nausea and vomiting and evidence of spontaneous extra-intestinal bleeding are among the more revealing associated symptoms.

DIFFERENTIAL DIAGNOSIS

Once the history has been obtained in as complete detail as possible, it seems to us a useful procedure to consider the differential diagnosis under certain broad groups, although the distinctions are obviously artificial ones.

I. *Syndromes Characterized by the Passage of Bright Red Blood and Associated with Anal Pain*

In this group one might include: (i) Fissure-in-ano. (ii) Fistula-in-ano. (iii) Rectal prolapse. (iv) Hemorrhoids. (v) Rectal foreign body.

Diagnosis here is seldom difficult and can usually be very simply confirmed by examination of the perianal area and digital examination of the rectum.

Of this group fissure-in-ano is by far the commonest lesion. Out of 36 cases discharged from the Edmonton General Hospital over the last nine years with a diagnosis of rectal bleeding, 26 or 72% were due to demonstrable anal fissures. In office practice the preponderance is even greater. Fissures appear to occur in two forms:

1) Multiple minute superficial erosions which are commonly seen in association with infantile diarrheas, debilitating illnesses and where poor perianal hygiene is apparent. Ten such cases were recorded but doubtless many more occurred which went unmentioned in the discharge summary and were therefore uncoded. The average age of these patients was 9 months and the average duration of symptoms 4 weeks. In this type of case the fissuring was usually of secondary importance, the blood loss was minimal, and the erosions rapidly healed when the primary condition was corrected. Among the measures utilized to minimize the perianal irritation, fastidious local hygienic measures, various analgesics and antibiotic ointments and exposure to a heat lamp seemed to be effective symptomatic measures.

2) In addition to the group with multiple superficial erosions were a group of 16 infants and children with the well marked symptomatology and physical findings of a single anal fissure as seen in the adult. In five of these the fissure had all the clinical features of a "chronic" anal fissure. The age range in this group was 6 months to 10 years with an average of 4.4 years. The duration of symptoms varied from one month to nine years. Four of the five patients with chronic fissures underwent surgical excision. The remaining 11 cases had typical single acute ulcers that responded to conservative treatment.

Typical of the monotonously similar case histories is that of a 7-year-old girl who was admitted to hospital in 1955. Her mother stated that she had tended to be constipated since birth and had complained of pain at the time of defecation for five years. This pain had been much more severe for the past two years and frequently the stool was streaked with a small quantity of bright red blood. For six months nocturnal anal pain had interfered with sleep. General examination was negative. Marked anal spasm was present but a deep indurated anal fissure could just be seen in the midline posteriorly. The day after admission excision of the fissure and anal dilatation was carried out and she was discharged two days later. There was no mention of any anal complaints when this girl was re-admitted one year later because of an upper respiratory tract infection.

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There were no cases of fistula-in-ano or hemorrhoids in the charts reviewed and these conditions are noted by most writers to be extremely uncommon in infants and children. The diagnosis is relatively simply confirmed by inspection, rectal and anoscopic examinations.

Cases of bleeding due to foreign bodies inserted into the rectum have been recorded in the literature although we found none among our cases. The diagnosis is apparently invariably made on rectal examination and removal results in complete cure.

Three cases of bleeding associated with rectal prolapse occurred in the University of Alberta Hospital series but the bleeding was minimal, often noted only as a slight ooze on the toilet tissue, and was invariably an inconsequential accompaniment of the obvious primary condition. Replacement of the prolapse and regulation of bowel function, with or without strapping of the buttocks depending on the laxity of the sphincter, resulted in cure of the bleeding along with cure of the prolapse.

II. *Syndromes Characterized by the Passage of Bright Red Blood Without Associated Symptoms*

Foremost among this group are: (i) Solitary and multiple juvenile polypi. (ii) Multiple familial polyposis. (iii) Chronic recurrent sigmoid intussusception. (iv) Neoplasms. (v) Meckel's diverticulum.

Rectal polypi are probably the commonest cause of painless bleeding per rectum in infants and children. In the University of Alberta Hospital series of patients with proven bleeding polypi the age varied from 3 months to 8 years with an average age of 2.7 years. There was an equal distribution between the two sexes. In these 12 cases the polyp was palpable on rectal examination in nine and found only at sigmoidoscopy in three. Barium enema examination was done in nine patients, but only in three of these was there any radiological evidence of polypi.

The following case history is representative. At 3 years of age this boy had never had a sick day. In the five-week period prior to his admission to hospital his mother noted a small quantity of bright red blood on the surface of his stool on three occasions although the child had no spontaneous complaints. His two older brothers and his parents had never had any bowel complaints. On examination a mobile, pea-sized polyp was readily palpable at fingertip level in the rectum. The long pedicle appeared to arise from the posterior anal wall. Unlike most of the cases of polypi, barium enema examination in this case did demonstrate the polyp. The hemoglobin was 13.3 g. or 91% of normal. At sigmoidoscopy under general anesthesia the polyp was seen readily 4.5 in. from the anal margin and the pedicle sectioned at its base with a coagulating Frankfeldt snare. The pathological report was ulcerated benign rectal polyp of the juvenile type, 1 cm. in diameter. There was no history of further bleeding episodes when he was re-admitted for tonsillectomy at age 6. Although the bleeding in this case was minimal it should be noted that on occasion it can be massive. Two of the 12 cases presented with exsanguinating hemorrhage which necessitated immediate transfusion and resuscitative measures.

The occurrence of multiple polypi of the juvenile type should not be confused with the distinct entity, multiple familial polyposis. In the former instance there is said to be no risk of malignant transformation and local excision is the ideal treatment. The one such case that occurred in this series warrants brief comment.

In 1954, this 3-year-old girl was admitted to hospital for investigation of rectal bleeding of sufficient severity to depress her hemoglobin to 10.6 g. or 73% of normal. A palpable polyp at 5 cm. was removed through the sigmoidoscope and two other polyps that had been demonstrated by barium enema in the sigmoid colon were removed by laparotomy and colotomy. Re-admission for investigation of persisting episodes of bright red rectal bleeding 8 months later revealed no source of bleeding. She was admitted again in 1958 when she was 7 years of age because of a two-day history of profuse rectal bleeding. Her hemoglobin on this occasion was 9.4 g. or 65% of normal. After blood transfusions had restored her blood volume to normal barium enema examination revealed the presence of four polypi. One polyp at 3 cm. was removed through the sigmoidoscope and three at laparotomy and colotomy, one in the sigmoid colon and two in the transverse colon. All polypi were of the juvenile type. There has been no further bleeding in the last three years.

There were no cases of multiple familial polyposis in this series. It is of interest to note that although this disease is hereditary it is not congenital. Seventy-seven per cent of the cases in the 1951 series from the Mayo Clinic[9] occurred between the ages of 20 and 39 years and only 8.4% occurred before the age of 20. The series of McKenney[10] had a somewhat higher incidence in childhood, five of his 21 cases occurring before the age of 12. Eighty per cent of the 95 cases reported by the Mayo group had rectal bleeding and diarrhea was a common associated symptom. Multiple familial polyposis must, of course, be recognized for what it is, a premaligant lesion. The high incidence of malignant transformation makes radical surgical excision mandatory.

One should possibly mention, in passing, the rare Peutz-Jeghers syndrome in which gastrointestinal polyposis is associated with patchy melanin pigmentation of the oral mucosa. While the polypi in such cases are characteristically situated in the small intestine and the clinical presentation is usually that of small bowel obstruction, rectal bleeding occurs with considerable frequency. In 60% of the 52 cases collected by Staley and Schwartz[12] the onset of symptoms was before the age of 20 years.

Chronic recurrent sigmoid intussusception was not recognized in any of our cases and is, as far as can be determined, a new entity described by Kiesewetter, Cancelmo and Koop.[6] They suggest that in some children the normal redundancy of the sigmoid colon is exaggerated allowing it to intussuscept into itself on straining. The intussusception is asymptomatic unless the succulent leading point is traumatized by the presence of constipated stool giving rise to minimal bright red bleeding. The diagnosis is made by observing the intussusception through an adult sigmoidoscope and the treatment involves bowel training and softening and lubricating the stool by means of oral mineral oil. Kiesewetter believes this type of lesion accounted for the symptoms in 18 of 143 "rectal bleeders" investigated by him.

Benign and malignant neoplasms may occur in the large and small bowel of infants and children and although such lesions are extremely rare in this age group no consideration of rectal bleeding would be complete without mention of this possibility. In this connection it is of interest to note that "bleeding is very unusual (in children with colonic carcinoma) in contrast to adults in whom it is the most common finding."[13]

Probably the most common childhood tumour of the gastrointestinal tract which may give rise to bleeding, often profuse, is the angioma. In addition to the angioma many would also classify under tumours of the gastrointestinal tract a wide variety of angiomatous conditions which might better be classified as systemic diseases or congenital vascular anomalies. Shepherd[11] in a very beautifully illustrated paper has classified these lesions occurring in the gastrointestinal tract as follows:

(1) *Osler-Rendu Disease* (Heredity Telangiectasis of the Skin and Mucous Membranes)

Clinically this disease is characterized by recurrent epistaxis and the appearance of angiomatous lesions of the skin of the face and mucous membranes of the nose, tongue and lips. It is of particular interest to the surgeon because it is frequently complicated by profuse rectal bleeding from similar visceral lesions. A family history is frequently obtained.

(2) *Parkes Weber-Klippel Syndrome* (Hemangiectatic Hypertrophy of the Limbs)

This syndrome is occasionally complicated by visceral angiomatous lesions.

(3) *Solitary or Multiple Angiomatous Lesions of the Gastrointestinal Tract*

The extreme difficulty encountered in the diagnosis and treatment of such lesions has been impressed upon us by the recent occurrence of two such cases in children in the Edmonton area. Both were males with exsanguinating rectal bleeding in whom the diagnosis of angiomatous malformation was made only at laparotomy. In both, recurrent hemorrhages have occurred which, to date, have been successfully treated by blood transfusion without further surgical intervention. In neither of these cases were cutaneous or naso-oral telangectasis present, nor was there involvement of the limbs. The future of these unfortunate children is uncertain.

A Meckel's diverticulum accounted for five of 113 cases of rectal bleeding reported by Kiesewetter, Cancelmo and Koop.[6] At the University of Alberta Hospital, this lesion has been recognized and removed from only 13 children under 16 years of age in the last 10 years. In five of these the removal of the diverticulum was incidental, the laparotomy having been performed for some other disease. In eight the diverticulum was the site of the pathology which made surgery necessary, four because of bowel obstruction, three because of hemorrhage and one because of acute inflammation. In the series reported by Gross,[5] bleeding was the commonest presenting symptom and occurred in 33% of a group of 149 children. Eighty per cent of the patients in Gross's series were under two years of age and the patients in this area presenting with bleeding were all under one year of age. The usual sex incidence of Meckel's diverticulum is about 70% males to 30% females, but all patients below the age of 16 at the University Hospital were males.

The following case history is classical except that during the minor prodromal bleeding episodes, which are frequently absent, the bleeding is more commonly dark in colour.

This 9-month-old male child was admitted to the University of Alberta Hospital in August 1959. The infant had been perfectly well all his life although his mother had occasionally noted small amounts of bright red blood mixed with the stools during the preceding five months. On the day of admission two large loose bowel movements, apparently composed completely of bright red blood, were passed and the child showed evidence of moderate shock. Blood was administered by the family doctor, and the child referred to the city. On arrival there were no physical findings of note except that the child was pale and bright red blood was noted mixed with the stool on rectal examination. The hemoglobin was 8.7 g. or 60%. An additional 600 c.c. of blood was administered in three transfusions over the next 36 hours by which time the stool was normal in colour and the hemoglobin was 83% of normal. Barium enema examination was negative and four days after admission, at laparotomy, a Meckel's diverticulum was discovered and excised. The specimen demonstrated an ulcer at the base of the diverticulum 5 mm. in diameter. The child's postoperative course was quite uneventful and there have been no further episodes of bleeding.

III. *Syndromes Characterized by the Passage of Bright Red or Dark Blood in which the Associated Symptoms are of Prime Concern and Importance*

In this group are included: (i) Intussusception. (ii) Mesenteric Thrombosis. (iii) Volvulus. (iv) Colitis. (v) Peptic Ulceration.

Little need be said here about the first three in this list, for the clinical syndrome is quite characteristic and the rectal bleeding is usually, although not invariably, a relatively minor consideration.

The occurrence of severe episodic abdominal pain in a child 3 to 11 months of age associated with vomiting, pallor and followed by the passage of the typical "current jelly" stool is diagnostic of intussusception when physical examination reveals a sausage-shaped mass in the right upper quadrant and an "empty" right lower quadrant. Mesenteric thrombosis is extremely rare in children but must be considered as a possible cause of strangulating obstruction with rectal bleeding. Midgut volvulus commonly occurs in the first three weeks of life and although profuse rectal bleeding has been recorded as the presenting complaint in this disease,[3] it is more commonly absent than present because the bleeding tends to occur into the closed loop rather than appearing at the anus. In any case the obstructive symptoms rather than the bleeding will be the outstanding feature of the disease. In all three of these diseases immediate surgical intervention is indicated except possibly in intussusception in which a barium enema may be a therapeutic as well as diagnostic maneuver.

A brief word may be in order referable to colitis as a cause of rectal bleeding. Many children pass small amounts of blood along with loose stools in acute non-specific enterocolitis. Of more importance and significance is the protracted passage of blood, pus and watery stools in cases of the specific dysenteries, amebic and bacillary. One must add to this list chronic idiopathic ulcerative colitis,[4, 8] for though more common in young adults this disease is being reported with increasing frequency in infancy and childhood. Its recognition in this age group is of particular importance because chronic ulcerative colitis may be associated with retardation of growth and development and demand consideration of extensive surgical resection before the age of puberty.

Duodenal ulcer, like idiopathic ulcerative colitis, is a disease that is being recognized to occur in infancy and childhood with increasing frequency.[2] The single case to come to our attention in the University of Alberta Hospital records was a male child who was first seen at age 22 months with a history of abdominal pain, melena and a single episode of massive hematemesis. No definitive diagnosis was reached during that admission and the child was discharged. However he continued to pass tarry stools intermittently. The child was readmitted three months later because of recurrent hematemesis and at laparotomy the only lesion present was an inflammatory reaction in the serosa of the first portion of the duodenum consistent with the presence of an underlying peptic ulcer. He was subsequently placed on a rigid ulcer regimen and has remained well for the last six months without further evidence of bleeding.

IV. *Syndromes Characterized by the Passage of Altered Blood Per Rectum Without Associated Symptoms*

In this group one might include: (i) Swallowed blood. (ii) Swallowed foreign body. (iii) Esophageal varices. (iv) Reduplications of the bowel, although it is appreciated that the speed of transit of the blood through the bowel may well be sufficiently rapid to give rise to red rectal bleeding.

Swallowed blood may appear at the anus after bleeding from the nose, or surgical or accidental trauma to the nose and mouth, in which case the origin is obvious. The blood usually is intimately mixed with the stools, small in amount and black in colour. Of more interest and possible confusion is the swallowed blood syndrome observed in the newborn. Maternal blood swallowed by the infant at the time of delivery characteristically appears as a reddish stool within seven to 30 hours after birth. Because this occurrence may be confused with hemorrhagic disease of the newborn it is useful to observe the action of alkali on the blood passed.[1] Alkali denatures adult hemoglobin to a brown colour while fetal hemoglobin retains its pinkish colour.

The swallowed foreign body as a cause of gastrointestinal bleeding is rare. This is truly remarkable when one considers the nature of the various articles which have passed through or been removed from the gut without the slightest evidence of mucosal laceration.

Portal hypertension with esophageal varices is not uncommon in children. It is more commonly due to an extra-hepatic block. While melena almost invariably accompanies bleeding from varices, the massive vomiting of bright red blood which almost inevitably occurs is by far the more prominent and outstanding symptom of the disease.

Duplications of the bowel are rare but when they occur in relation to the small bowel, the common site, bleeding per rectum may be the presenting symptom. The blood is usually small in amount, mixed with the stool and dark in colour though it may be massive and red in colour. Palpation of the abdomen may reveal the presence of a mass. Surgical excision of the duplication is the treatment of choice.

V. *Syndromes Characterized by the Passage of Altered or Bright Red Blood Per Rectum with or without Associated Symptoms*

In this miscellaneous group the systemic diseases, in which rectal bleeding may be one of, or the sole, manifestation of an underlying bleeding tendency, may be considered. While there are innumerable diseases which might be so classified one must be familiar with the five most commonly encountered, namely: (i) Hemorrhagic disease of the newborn. (ii) The purpuras, both nonthrombocytopenic and thrombocytopenic. (iii) Hemophilia. (iv) Scurvy. (v) Leukemia.

Hemorrhagic disease of the newborn is the commonest cause of gastrointestinal bleeding in the first week of life and is usually associated with bleeding from other sites. It is due to a multiple coagulation factor deficiency and is treated by the administration of vitamin K and fresh blood.

In the purpuras the rectal bleeding is usually only one of many hemorrhagic manifestations.

Recently a 10-year-old girl was seen who had an idiopathic thrombocytopenic purpura for four years and in whom a satisfactory remission had not been achieved with adrenal steroids. She was admitted to hospital with a 12-hour history of profuse bright red rectal bleeding. Her platelet count was 11,000 per c.mm. on admission and after a period of reassessment and preparation with several blood transfusions, splenectomy was performed. Her initial platelet response was most gratifying and the count returned to normal in seven days. It is now only seven months since her operation and we are anxiously following her progress in the hope that the remission will be maintained.

The diagnosis of hemophilia is usually suspected from the family history and the past history of previous hemorrhagic episodes. It is confirmed by the demonstration of the typical coagulation defect.

Scurvy is an uncommon disease today, but where avitaminosis is suspected as a cause of gastrointestinal bleeding the gums should be observed for evidence of vitamin C deficiency. Rectal bleeding not uncommonly occurs in leukemia but usually only late in the disease when the diagnosis is unfortunately all too obvious.

SUMMARY

The major etiological factors capable of producing rectal bleeding in infants and children have been reviewed and the features of some of these diseases have been illustrated with typical case histories. One must remember that this symptom, while often of little consequence, may well indicate the presence of a potentially lethal lesion. For this reason, the patient must be carefully investigated by means of a complete history and a painstaking physical examination, with special attention to the specific diagnostic features of those diseases capable of giving rise to this symptom. In addition, sigmoidoscopy, barium examination of the gastrointestinal tract and blood studies for coagulation defects will often be necessary to establish or confirm the diagnosis. Occasionally emergency laparotomy will be indicated for life-endangering massive hemorrhage where the preoperative work-up has of necessity been incomplete. In such cases an intimate knowledge of the many and varied pathological lesions capable of causing rectal bleeding and of their treatment may well be life-saving.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

PREVENTION OF ECLAMPSIA

Since it is late on in the toxæmia that the kidneys are affected, the examination of the urine for albumen as a guide to the condition is worse than useless. In most of the large modern clinics the urine is examined for urea. It matters not what the urea may be split up into, if the normal amount of about 472 grains a day be diminished it is necessary to give treatment to the patient or the condition may rapidly go on from bad to worse. I believe that this precaution is an absolute essential in every case of pregnancy, and symptoms of a toxæmia severe enough to kill may arise at any time after two and a half months, and some go as far as to say any time after six weeks.

Knowing that there are symptoms of toxæmia, however mild, present, which may rapidly grow worse, what treatment should be adopted? For very slight cases, probably calomel and soda, grs. ii, every second or third night, followed in the morning by a hot seidlitz, and the cutting out of meat and increasing the amount of milk taken, will be enough. In more severe types of toxæmia, it will be necessary to give the patient a hot pack one day and a purgative the next. Iron and digitalis, a skim milk diet and absolute rest in bed, are indicated. If the case becomes progressively worse and the treatment fails to improve the toxæmia, it then remains to consider seriously producing an abortion or premature labour.—H. L. Reddy, *Canad. M. A. J.*, 1: 1067, 1911.

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CASE REPORTS

COXSACKIE B5 VIRUS AS A CAUSE OF NEONATAL ENCEPHALITIS AND MYOCARDITIS*

D. M. McLEAN, M.D., W. L. DONOHUE, M.D., C. E. SNELLING, M.D. and J. C. WYLLIE, M.D., *Toronto*

ALTHOUGH numerous studies have demonstrated an etiological relationship between the Coxsackie B viruses and the syndromes of aseptic meningitis and pleurodynia, the association of these viruses with encephalitis and myocarditis of the newborn has been demonstrated infrequently.[1, 2] During the past decade, evidence of an etiological relationship between Coxsackie B3 virus and acute encephalitis and myocarditis of newborn infants was obtained after this syndrome was recognized in 10 babies in Johannesburg, South Africa, during October and November 1952.[3] In a subsequent outbreak of this syndrome in newborn babies in Southern Rhodesia during 1954, Coxsackie B4 virus was isolated from two of three affected infants.[4] In North America, somewhat later, Coxsackie B3 virus was isolated from the spinal cord of a 7-day-old infant who died with diffuse myocarditis and meningo-encephalitis.[5] By 1961, myocarditis had been reported in 45 newborn infants, 33 of whom died within the first two weeks of life, and in many instances Coxsackie B viruses have been isolated from tissues of affected infants.[1]

The present paper reports the clinical, pathological and virological findings in an infant admitted to the Hospital for Sick Children, Toronto, during May 1961; this child died on the thirteenth day of life with encephalitis and focal myocarditis. Isolation of Coxsackie B5 virus from brain, myocardium, lungs and liver of the infant confirmed that this virus had infected the child. Development of pleurodynia in the mother one day antepartum, together with an elevated Coxsackie B5 antibody titre in her serum nine days post partum, suggested that the infant contracted the Coxsackie B5 infection *in utero*.

The Present Case

On May 9, 1961, a full-term male infant with a papular rash on the trunk and limbs was born. He had normal physical activity, the suck was strong, and the appetite was satisfactory. The chest was normal on auscultation and the heart rate was 160 per minute with regular rhythm. On the fourth day of life the rash had disappeared but the child now had a temperature of 103° F. The following day, May 14, he was transferred to the Toronto Hospital for Sick Children with a temperature of 102° F. and irritability, twitching and fullness of the anterior fontanelle. Several loose brown stools were passed. Cerebrospinal fluid obtained by lumbar puncture contained 520 cells per c.mm., predominantly lymphocytes, and the Pandy test was strongly positive. Bilateral subdural taps yielded no fluid. The hemoglobin was 13.8 g. per 100 c.c.; the leukocyte count was 12,300 per c.mm. with the following differential: neutrophils 32%, band forms 2%, eosinophils 1%, lymphocytes 49% and monocytes 16%.

After May 14, the infant's temperature did not exceed 99° F. On May 18, he vomited continuously and passed several watery green stools; the abdomen was distended and soft, but there were no abnormal findings in the chest and heart on clinical examination. The cerebrospinal fluid contained 628 lymphocytes per c.mm. On May 19, neck stiffness was noted, the respiratory rate was 72 per minute, there was moderate indrawing of the chest, the heart rate was 180 per minute, and the liver edge was palpated 2 cm. below the right costal margin. On May 21, the heart rate was 160 per minute, the liver edge was palpated 4 cm. below the right costal margin, and the respirations were shallow and rapid at 80 per minute.

The infant died on May 22, 1961, at 13 days of age.

The mother of this infant was 21 years of age, had been pregnant twice and had one living child. She complained of gripping pains especially on the right side of her chest and abdomen immediately before and during labour although she did not have an elevated temperature. Her daughter aged 2½ years had fever, accompanied by vomiting, of one day's duration, three days before the birth of the infant described in this report. The father remained asymptomatic during this period. Labour proceeded normally, the membranes ruptured three hours before delivery, and forceps were applied after the infant's head had crossed the pelvic outlet.

Virological Investigations

Cerebrospinal fluid specimens obtained from the patient on the fifth and ninth days of life were examined for virus content by inoculation of trypsinized cultures of monkey kidney cells in roller tubes, as described previously.[6] Coxsackie B5 virus was isolated from both these specimens. No bacteria were cultured from these specimens of cerebrospinal fluid.

Portions of brain, heart, liver and lung were removed 20 hours after the infant's death. These were ground in mortars, and sufficient maintenance medium ELY was added to give approximately a 20% suspension. After centrifugation of these suspensions at 8000 revolutions per minute for 30 minutes, they were inoculated into monkey kidney tissue cultures. Coxsackie B5 virus was isolated from all four tissues in concentrations (TCD_{50} per gram) ranging from brain $10^{1.7}$ to heart and lung $10^{2.5}$ and liver $10^{5.0}$.

Specimens of sera obtained from the infant on the sixth day of life and from the mother nine days after delivery were examined for neutralizing antibody content to 100 TCD_{50} of Coxsackie B5 virus.[6] Serum from the infant contained no antibody, whereas antibody was detected in the mother's serum at titre 250.

*From the Departments of Virology, Pathology and Pediatrics, The Research Institute of the Hospital for Sick Children, Toronto.

Fig. 1.—Small inflammatory lesion just under the endocardium of the left ventricle.

Pathological Investigations

Naked eye examination of the tissues of this infant, including the central nervous system, disclosed no unusual features except for patchy areas of hemorrhages and atelectasis of both lungs.

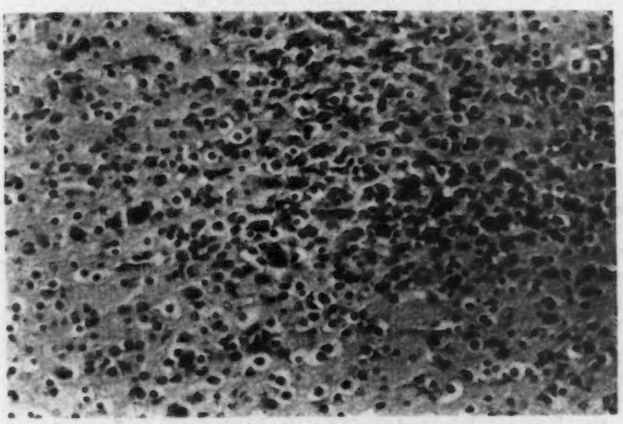

Fig. 2.—A focal but ill-defined area of degeneration in the cortex of the cerebrum.

Although the virus was isolated from the brain, heart, liver and lungs, significant microscopic lesions were present only in the heart and central nervous system.

In the heart, widely scattered microscopic lesions were present under the epicardium and in the myocardium of the right and left ventricle and the interventricular septum (Fig. 1). These lesions consisted of necrosis of myocardial fibres with an infiltration of mononuclear cells.

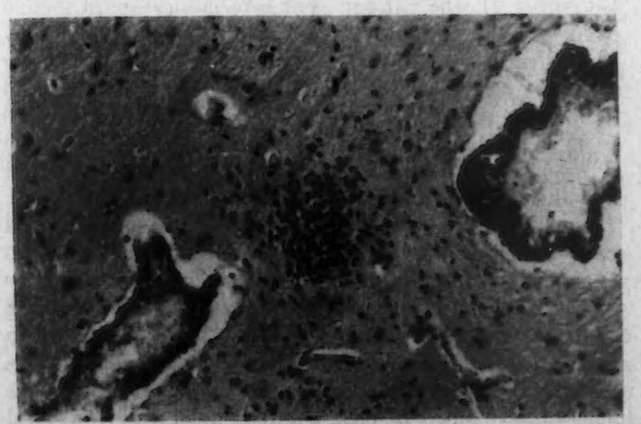

Fig. 3.—A glial knot and perivascular cuffing.

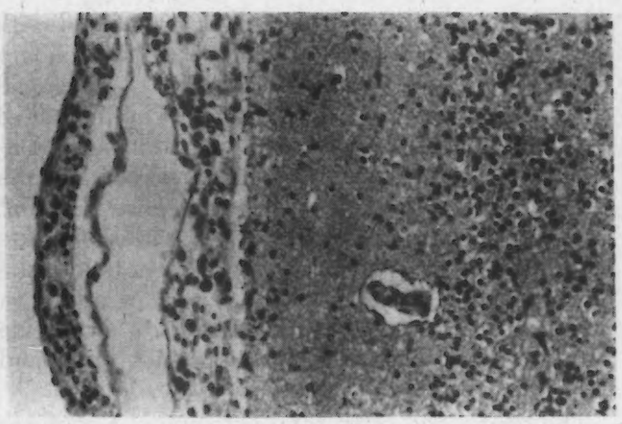

Fig. 4.—Cerebral cortex showing the meningitis.

In the central nervous system, lesions were present in the cord, medulla and cerebellum, but were not frequent. On the other hand, numerous focal lesions were encountered in the remainder of the brain; they were most prevalent in the basal ganglia. These lesions consisted of areas of eosinophilic degeneration of cortical cells (Fig. 2) with microglial reaction, the so-called glial knots and perivascular cuffing (Fig. 3). A meningeal reaction consisting mostly of mononuclear cells was most marked over the cerebral hemispheres (Fig. 4).

The lesions in the cortex were more destructive than those seen in the usual viral encephalitis; and they raise the question of permanent brain damage if the infant had survived. Otherwise the encephalitic lesions were in no way specific.

No lesions were present in the fat or skeletal muscles.

DISCUSSION

The rapidly downhill clinical course, accompanied by histopathological findings of encephalitis and myocarditis, fits the hypothesis that this infant contracted an intrauterine infection with Coxsackie B viruses, less than one week before delivery.[1] This diagnosis is confirmed by the isolation of Coxsackie B5 virus from brain, myocardium and other tissues of the infant who was less than two weeks of age and was born to a mother who had clinical and serological evidence of Coxsackie B5 virus infection in the immediate antepartum period. Although a rash has not been observed in most published reports of fatal neonatal Coxsackie B infections,[2] a petechial rash was noted over the trunk of one infant who died at 13 hours of age following infection with Coxsackie B4 virus.[7] Both parents and two other children of this family developed a respiratory illness nine days before the infant was born; the mother had pleurodynia seven days antepartum, and sera from both parents taken five days and 47 days after the infant was born contained elevated Coxsackie B4 antibody levels.[7]

The mother of a 3-day-old infant (who died with myocarditis and adrenal cortical necrosis secondary to a Coxsackie B3 virus infection[8]) developed pleurodynia four days ante partum. The mother of a 6-day-old infant (who died with diffuse meningoencephalitis and severe focal necrosis of the liver) had pleurodynia 24 hours post partum.[9] Aseptic meningitis due to infection with Coxsackie B4 virus occurred in a woman two days before she delivered; the infant died at 12 days of age with meningoencephalitis and myocarditis.[10] Coxsackie B4 virus was isolated from this infant's brain and myocardium.

The severe and often fatal outcome of Coxsackie B infections contracted by the fetus during the immediate antepartum period, contrasts sharply with the relatively benign course of Coxsackie B infections contracted post partum. For example, at the Hospital for Sick Children during 1959, Coxsackie B2 infections which caused aseptic meningitis in two infants, aged seven days and two months respectively, were followed by uneventful recovery of both patients. An infant who developed aseptic meningitis due to Coxsackie B5 infection during 1958 had completely normal mental and physical development on examination more than two years later. In older children the incidence of sequelae following aseptic meningitis due to infection with Coxsackie B viruses during the past three years has been negligible.

SUMMARY

A 13-day-old infant showed extensive encephalitis and some foci of necrosis of the myocardium following intrauterine infection with Coxsackie B5 virus. This virus was isolated from brain, myocardium, lungs and liver of the infant. The mother developed pleurodynia one day ante partum, and the presence of Coxsackie B5 antibody in her serum, obtained nine days post partum, suggests recent infection with this virus.

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HEMOLYTIC DISEASE OF THE NEWBORN DUE TO ANTI-Jk^a SENSITIZATION DURING PREGNANCY

E. T. MUTRIE, M.D., C.M., *Guelph, Ont.*

THE KIDD system of blood groups was discovered in 1951 when the antibody anti-Jk^a was identified. Anti-Jk^a and the antithetical anti-Jk^b provide evidence of two gene-products Jk^a and Jk^b and of four phenotypes Jk(a −b +), Jk(a +b +), Jk(a −b +, and Jk(a −b −). In about 18% of random matings, the mother will be Jk(a −b +) and the father will carry the incompatible antigen Jk^a.

Despite the apparent risk of feto-maternal incompatibility due to anti-Jk^a, the reported clinical problems due to this antibody are few. Immunization by Jk^a during pregnancy has been described by Hunter, Lewis and Chown,[3] as well as by others[4-6] but only three cases of hemolytic disease of the newborn due to such incompatibility have been reported[1,7,8]: and in only one of these was an exchange transfusion required.[8] A further case requiring exchange transfusion is described here.

Mrs. R., a 29-year-old Dutch woman, was seen on May 29, 1958, early in her first pregnancy. She had enjoyed good health all her life; her last menses was on March 1, of that year and her estimated date of confinement was December 8, 1958. Her prenatal course was uneventful; a Wassermann test performed on her serum was non-reactive and she was Rh positive. Fetal movements stopped 10 days after her expected date of delivery; the patient's serum fibrinogen levels were within normal limits and she gave birth spontaneously to a dead fetus on January 4, 1959. The fetal death was attributed to strangulation *in utero* by a short umbilical cord, which was found about the stillborn's neck. This woman returned on July 20, 1959, for care during her second pregnancy; her last menses was on May 1 and her estimated date of confinement was February 5, 1960. Her prenatal course was uneventful, but on December 16 fetal movements ceased; serum fibrinogen levels at this time were within normal limits. On December 21, the patient went into labour and a second child was delivered stillborn, after 33 weeks' gestation. The direct Coombs' test on cord blood one week after death *in utero* was strongly positive. Both mother and father were group O Rh positive. The mother was grouped as O *NsNs* P_1 *DCe/DcE* K+K+Le(a−) Fy(a+b−) Jk(a−); reports from two laboratories[9,10] suggested that anti-Jk^a and anti-S were present in the maternal serum.

The patient became pregnant again late in 1960 and was seen on December 8, 1960. Her last menses was on August 4 and the estimated date of confinement was May 12, 1961. In view of the previous history, it was decided to carry out a Cesarean section after 34 weeks' gestation followed by an immediate exchange transfusion, if the baby could be kept alive *in utero* until that time. This plan was explained to both the patient and her husband and they agreed with it.

On April 7, 1961, she was admitted to hospital. On examination the fetal heart sounds were well heard but the cervix was not dilated by rectal examination despite the patient's complaint of cramp-like pains. The opinions of specialists in surgery, anesthesia and pediatrics were sought to confirm the need for a classical Cesarean section, to provide for an appropriate sedation and anesthesia and to plan the details of immediate postpartum care; the last would include an immediate exchange transfusion if the Coombs' test performed on the infant's blood was positive.

At approximately the 35th week, a classical Cesarean section was performed, and a male infant weighing 6 lb. ½ oz. was delivered. A direct Coombs' test performed on the cord blood was positive; the hemoglobin and bilirubin levels of the cord blood were 13.6 g. and 0.8 mg. % respectively. The infant had a degree of pulmonary atelectasis but the pediatric consultant did not feel that this was a contraindication to an exchange transfusion. This was immediately performed, using 450 ml. of O Rh positive blood which was compatible by the indirect anti-globulin method. The baby's serum bilirubin rose to a peak of 8.8 mg.% on the sixth day; the hemoglobin was 13.3 g.%; but no evidence of kernicterus was seen although the child was slightly jaundiced at that time. Five weeks after birth, the hemoglobin had fallen to 8.3 g.%, the serum bilirubin was 4 mg.% and a simple transfusion of 100 ml. of Rh positive blood was given which was compatible by the indirect antiglobulin method. The baby was discharged with a hemoglobin of 14.0 g.% and a hematocrit of 40% and has done well since.

Discussion

Serology: The phenotypes of the parents and of the baby are as follows:

Mother:
O *NsNs* P_1 *DCe/DcE* K+k+ Le(a−) Fy(a+b−) Jk(a−)

Father:
O *MsNs* P_1 *DCe/DCe* K−k+ Le(a−) Fy(a+) Jk(a+)

Infant:
O *MsNs* P_1 *DCe/DcE* K+k+ Le(a−) Fy(a+) Jk(a+)

In the maternal serum, anti-Jk^a (p = 1/715) and anti-S (p = 1/75) were present. Since the infant is S-negative, only the maternal anti-Jk^a could have been responsible for the hemolytic disease.[11]

The opinion of a consultant in hematology was sought regarding the interpretation of this unusual series of events. He said that the findings could reasonably be interpreted as indicating that the mother became sufficiently sensitized to the Kidd antigen of the red blood cells of the fetus to produce hemolytic disease of the newborn. The mother was sensitized by Jk^a and S antigens, but the baby was S− (ss) and only its Jk^a antigen was affected by the maternal anti-Jk^a. This circumstance is exceedingly rare, there being only three other reported cases and only one other in which exchange transfusion was required.

Summary

An unusual situation is described in which a young woman suffered the loss of her first two pregnancies due to the intra-uterine fetal death from anti-Jk^a sensitization and hemolysis. A healthy male child was delivered at her third pregnancy by elective Cesarean section in the 35th week and was treated by means of an immediate (? total) exchange transfusion. This is the third such case reported and only one other was treated by exchange transfusion.

The author wishes to acknowledge the advice and assistance of Drs. W. A. Scott, F.R.S.(C), A. B. McCarter, J. J. Brown and E. L. Barton and the laboratory staff in their respective fields of general surgery, anesthesia, pediatrics and pathology at St. Joseph's Hospital, Guelph; also, Drs. W. D. Wigle, J. K. Ingham and P. Levine for interpretation of the blood types, and Dr. B. P. L. Moore for advice and assistance in the preparation of the manuscript.

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SHORT COMMUNICATION

PHOTOGRAPHIC ILLUSTRATION FOR MEDICAL WRITING*

IV. GROUPING AND FINISHING PHOTOGRAPHIC ILLUSTRATION FOR PUBLICATION

DONALD J. CURRIE, M.D. and
ARTHUR SMIALOWSKI, *Toronto*

Illustrations, in addition to attracting attention and arousing interest, are informative, but there is a limit to the amount of information which a single photograph can record. More information can be portrayed by a group of photographs. A group of suitable and related photographs can be combined by an author or publisher. Grouping is the technique of combining two or more photographs into one illustration. Grouping creates a compact picture story which presents a great deal of information attractively and concisely. Grouped photographs are reproduced as a unit, and the cost of publication is greatly reduced.

Suitable photographs showing several different aspects of the same subject, different fields or different appearances at different times may be grouped. Grouped photographs may show a sequence of events such as a maneuver or a procedure. Related medical photographs may be grouped showing the patient, the gross appearance of a disease, and the microscopic and radiographic appearances of the part. Comparisons may be facilitated by showing several diseases, deformi-

*From the Departments of Surgery and Photography, St. Michael's Hospital, Toronto.
This is the fourth in a series of five communications which are being published in successive issues.

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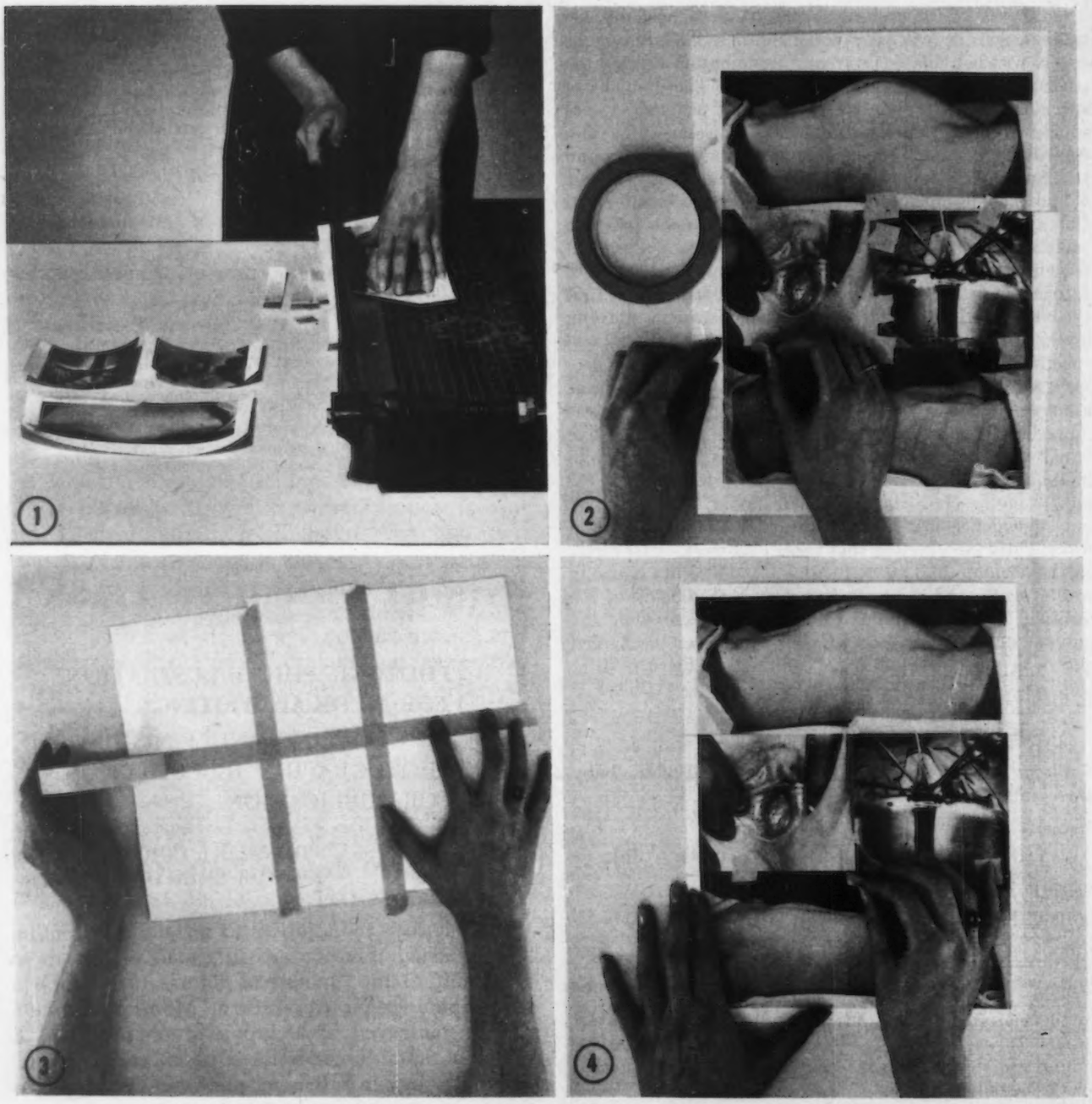

Fig. 1.—Grouping photographs. (1) The prints are trimmed properly. (2) The prints are joined and temporarily held by short pieces of tape. (3) The grouped illustration is turned over and the joins are firmly fixed by applying strips of tape. (4) The short strips of tape are removed from the surface of the grouped illustration. The white borders are trimmed evenly. Grouped photographs of hematocolpos due to imperforate hymen show the distended abdomen, the bulging intact hymen, the draining blood and the postoperative appearance.

ties, defects or procedures. The combinations of available material are almost without limit.

Good grouping is the result of careful planning of photographic material. Grouping should be the responsibility of the author because he is the one most familiar with the subject matter and should know the best way to present his material. The author should always bear in mind the advantages of grouping while planning, ordering and submitting his illustrations for publication. A publisher who receives photographs which are not grouped is at a disadvantage because of the fact that he is not familiar with the subject matter and because of the likelihood that the photographs were ordered and taken without a plan for grouping in mind. If the author has a plan for grouping, he need not do the work himself, but he will be able to help the publisher or photographer by providing detailed instructions.

PLANNING

Photographs for grouping should be taken especially for this purpose and they must be planned in detail for continuity, relationship and size. These photographs should have certain common features. They should be of similar or related size and uniform background and be made by similar photographic techniques. A uniform appearance of all illustrations is always desirable, and uniformity is easily maintained if all of the photographic work

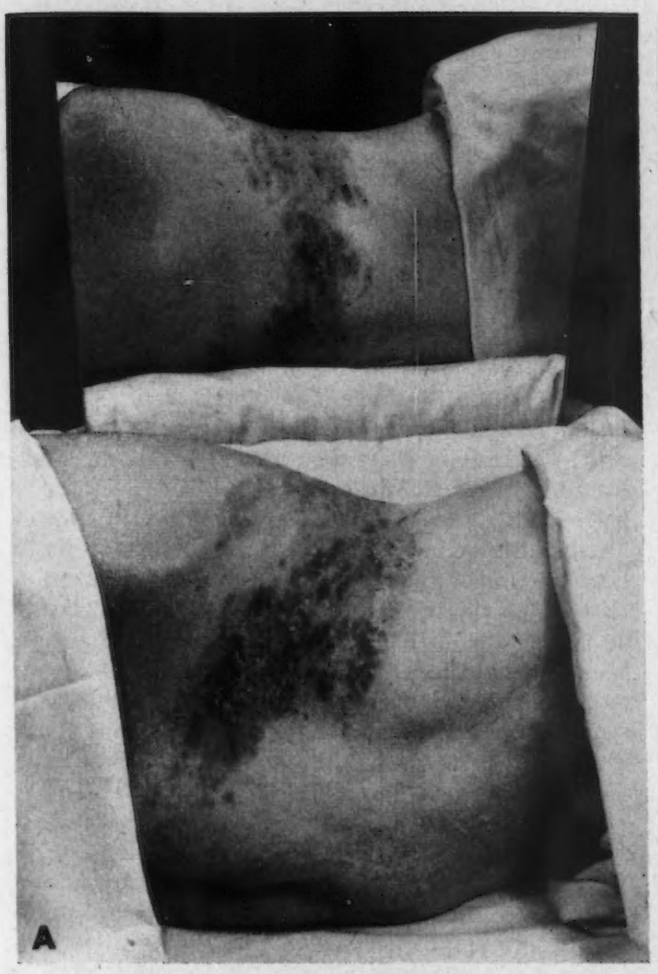

Fig. 2a

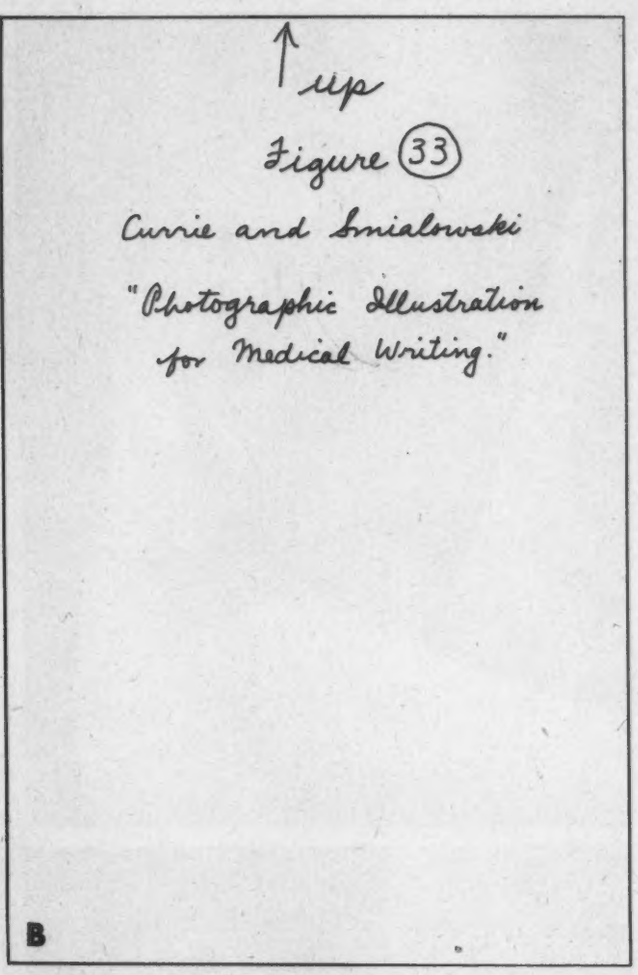

Fig. 2b

Fig. 2a.—Mirror-subject photograph showing simultaneously a front view and a mirror image of the back of a patient suffering from herpes zoster. **Fig. 2b.**—Is the reverse side of the photograph, showing proper identification. The top is indicated by an arrow and the word "UP". The figure number identifies the illustration and the legend which is always submitted separately. The author's name and the title of the article or book completes the identification.

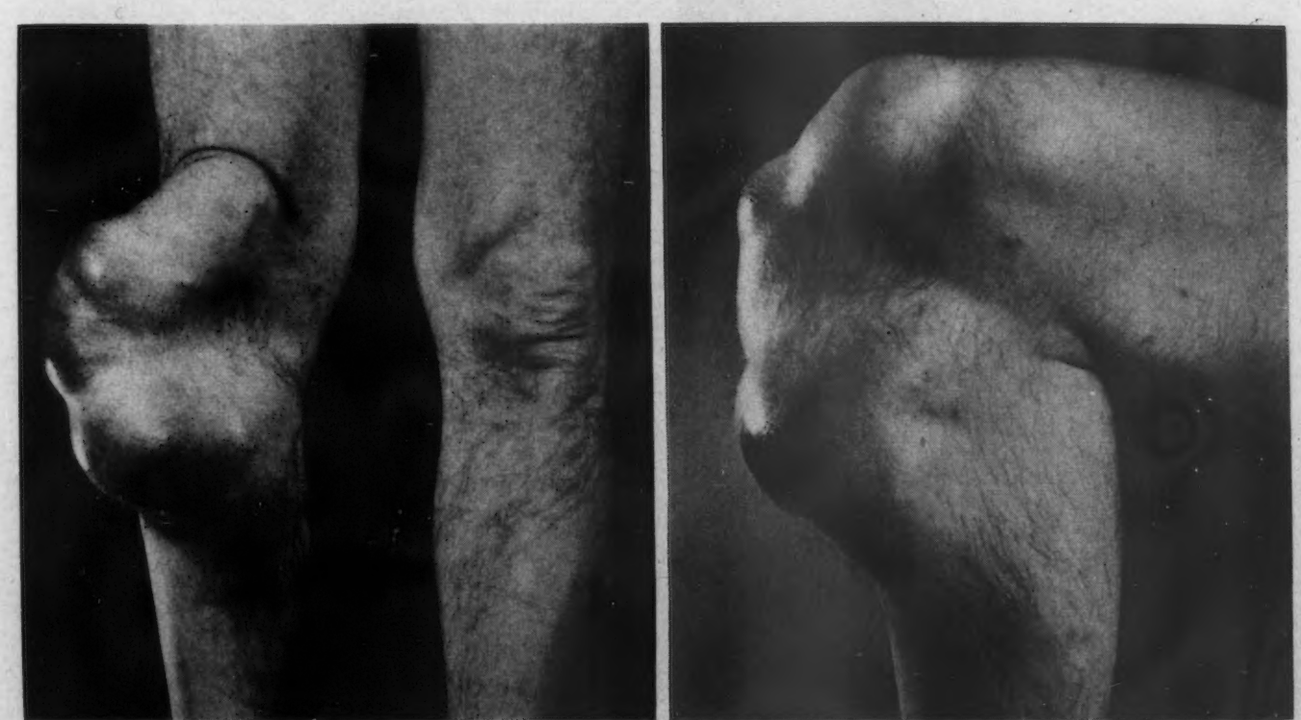

Fig. 3.—Large prepatellar bursitis complicated by hemorrhage and successfully treated by surgical excision. Two photographs taken from different points of view should be grouped, as they are related and can be compared easily.

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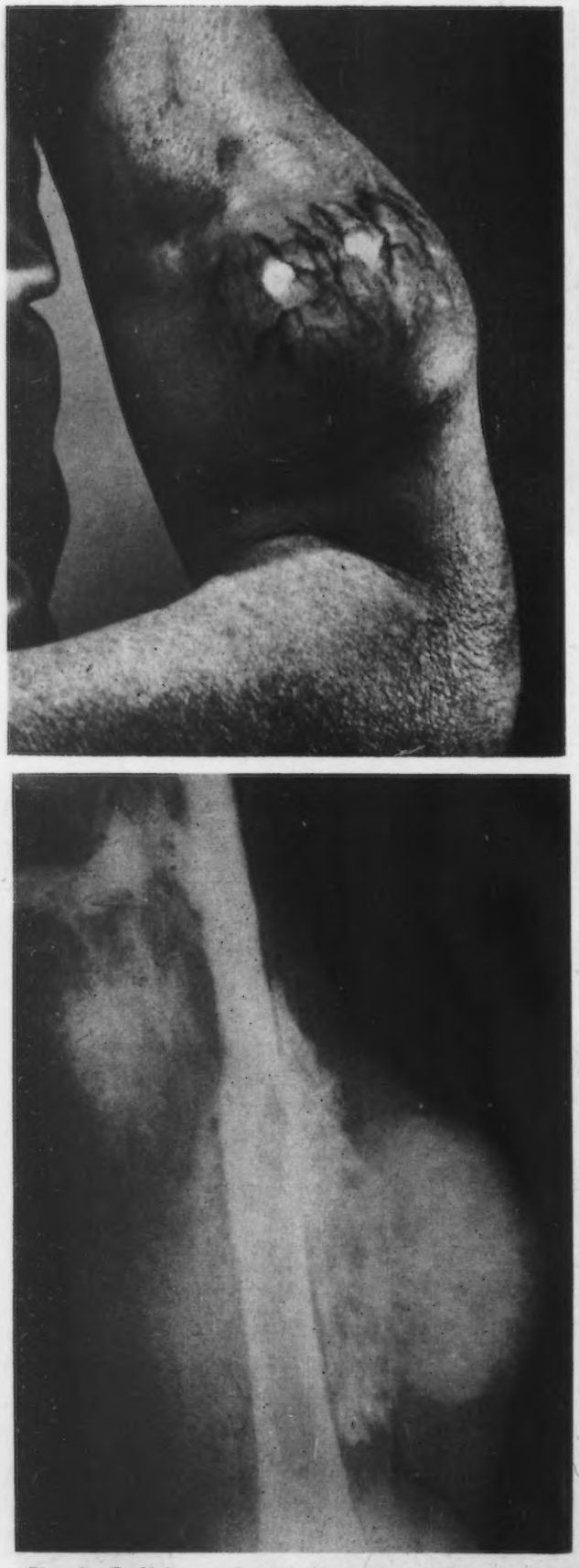

Fig. 4.—Ossifying periosteal fibrosarcoma. Twenty years ago the upper half of the humerus was excised because of a tumour arising from the bone, and the defect was repaired by a graft taken from the fibula. The clinical picture shows the recurrent tumour in the lower half of the humerus. The radiograph shows the ossification and calcification caused by the recurrent tumour. Vertical grouping of photographs is suitable for the double column page. Because of the distinct difference between the two photographs and adequate legend, distinguishing letters or figures were not needed.

is carried out or supervised by one photographer. Uniformity of illustrations facilitates grouping.

SIZE OF PRINTED PAGE

The medical author will have chosen the journal in which he would like his writing to be published, in most instances. He should obtain a copy of the journal and measure the area covered by print. He should then make a reference outline of the area of print for this page, but about 30-50% larger. This outline will help the author, photographer and artist in planning the size and proportion of the illustration to fit the page. A medical journal printed with two or three columns to a page permits greater flexibility in arranging illustrations. Where a large legend is intended or a large illustration is planned which might almost fill the printed area of a page, the author should bear in mind that space below the illustration should be allowed for the legend. If the journal in which the article is to be published has not been decided upon, photographs should be in standard sizes not smaller than 4 x 5 inches and not larger then 11 x 14 inches. Photographic negatives should always be kept; new prints may have to be made for grouping.

In preparing illustrations for a book, the author should determine as early as possible the size of the page and number of columns. Once these are determined, the illustrations can be made oversize but in correct proportions to fit the page. If they cannot be determined early in the writing of the book, the grouping of photographs should be delayed until the page size is known.

The author will profit by reviewing previous copies of the journal which he has chosen for his publication. The author of a book will be guided by similar volumes sold by his publisher.

MARKINGS

Grouped photographs must be properly identified and should follow a certain sequence, usually left to right and top to bottom. Where there are only two views, they may be identified in the legend as "left" and "right" or "top" and "bottom". In other instances separate legends under each photograph may be used. Where photographs are characteristic and fully explained in the legend, such as clinical views, radiographs or microscopic fields, separate markings on the face of each photograph are not needed. In all other cases, individual components should be numbered or lettered in sequence for identification in the legend and occasionally in the text. The word "figure" never appears in the illustration with the sequence letter or number.

IDENTIFICATION

Each illustration must be identified on the reverse side of the print. The identification may be written lightly in pencil with the face of the photo-

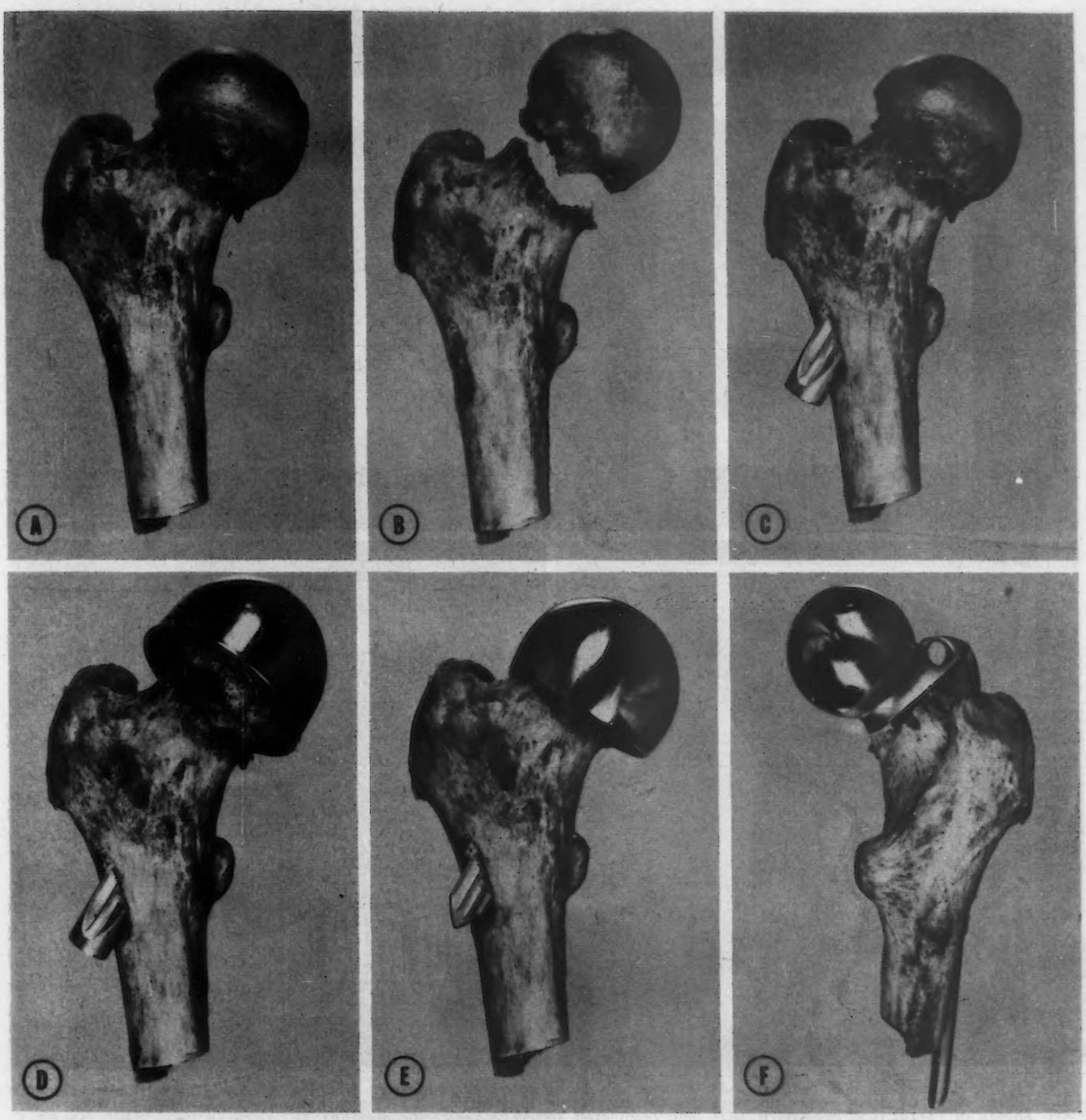

Fig. 5.—Fracture of the neck of the right femur. The series of photographs demonstrate the reduced fracture, the fragments displaced. Smith-Petersen nailing, S.-P. nailing and cup arthroplasty, Judet-type vitallium prosthesis and an Austin-Moore prosthesis. In planning this illustration, the same photographic technique was used for each photograph. The individual photographs were enlarged and cropped for ease in comparison and marked in orderly sequence.

graph on a hard smooth surface such as glass to protect the emulsion from pencil impressions. Occassionally the identification markings may be written in ink or by typewriter on a separate piece of paper which is stuck to the reverse side of the print by tape. Since many medical subjects are not easily recognized, an arrow should be drawn on the reverse side pointing to the top of the illustration, and the word "UP" should be written beside it. This will prevent the printer from placing the illustration on its side or upside down. Every illustration must be marked, whether or not such marking seems important. The figure number is recorded and it should be checked to ensure that it corresponds with the correct legend. Legends are never written on the reverse side of the illustration but should be submitted separately with the text, to be set into type. The author's name and the title of the article or book are recorded to identify the illustration should it be misplaced by the editor or publisher.

GROUPING PHOTOGRAPHS

A large print trimmer, scissors, tape and a ruler are required for trimming and joining prints in groups. The trimmer must be large enough to handle the largest prints and such an instrument is necessary for straight, clean cuts. It is not pos-

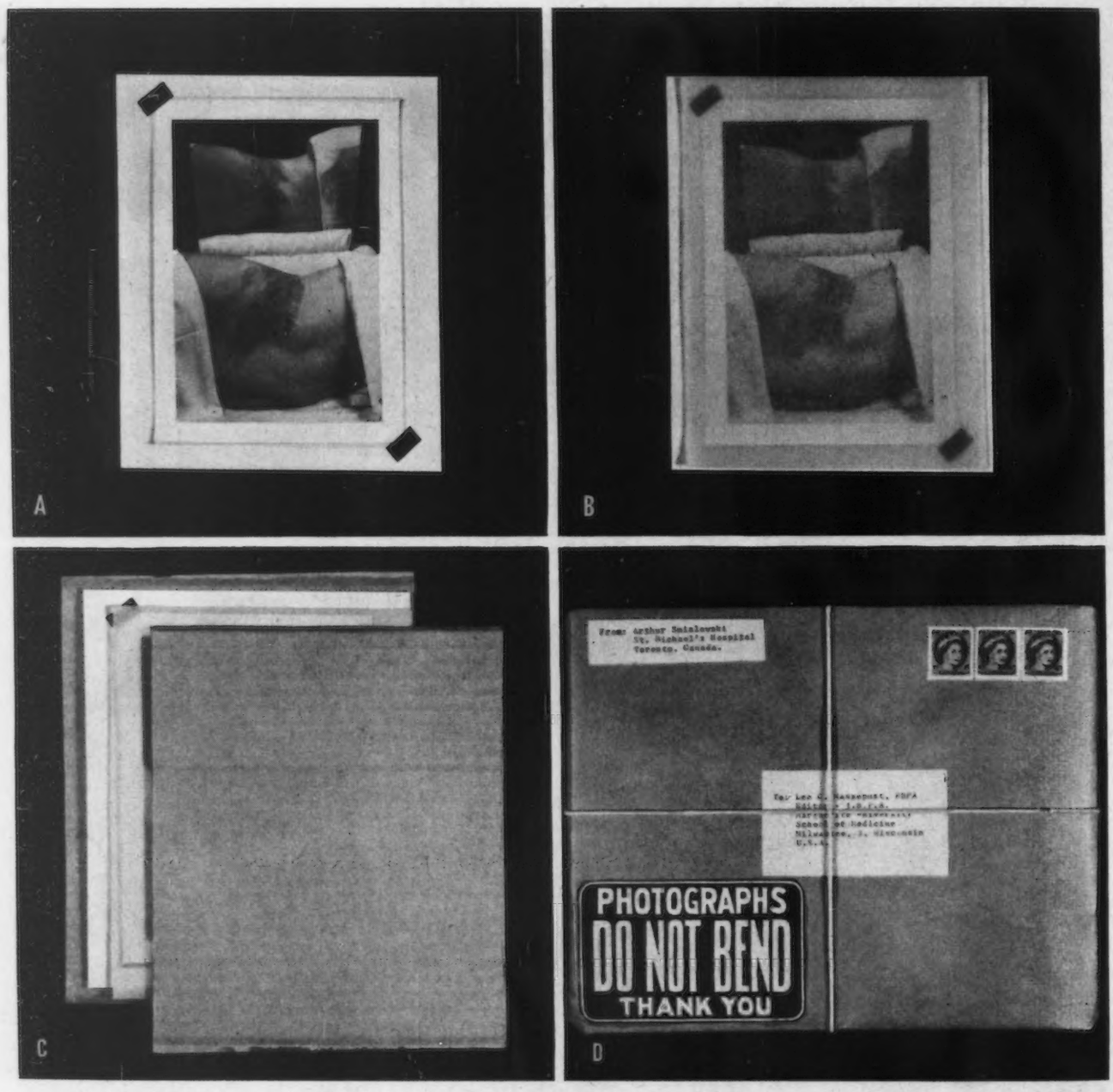

Fig. 6.—Packaging and mailing. (A) Photograph is attached to cardboard by tape at the corners for protection. (B) A clean sheet of tissue paper protects the surface of the illustration. (C) Photographs are sandwiched between oversized sheets of corrugated cardboard. (D) The completed parcel is ready for mailing.

sible to cut photographs with a pair of scissors or a blade with sufficient accuracy for joining in grouping. Autoclave tape is self-adhesive, easy to apply and remove, and is easily cut with the trimmer or scissors. A grease pencil may be used to make guide marks on the glossy surface of prints, because the marks can be removed easily by wiping and the glossy surface will not be damaged. A soft pencil may be used for a matte surface, but a grease pencil should not be used here, as the marks are difficult to erase. A large work bench with a transilluminated opal screen will be very helpful in arranging photographs for grouping.

Grouping of photographs may be possible only if the author and photographer have carefully planned the illustrations. The cost of publishing a grouped illustration is less than the cost of publishing the individual photographs. Simple grouping of several photographs may not require careful planning, but the grouping of a number of photographs may be possible only if it is carefully planned.

Grouping may be performed by the author, photographer or publisher. Photographic prints of the correct size for the grouping are prepared. The prints are properly trimmed, fitted together and held by short pieces of tape on the emulsion surface of the photograph. The author must be certain that the edges are joined accurately. A white border line should never be left between the prints. A white dividing line is added by the engraver. The joined illustrations are turned over to lie emulsion-side down. Tape is used to fix the prints together along all joined edges. The emulsion side is again

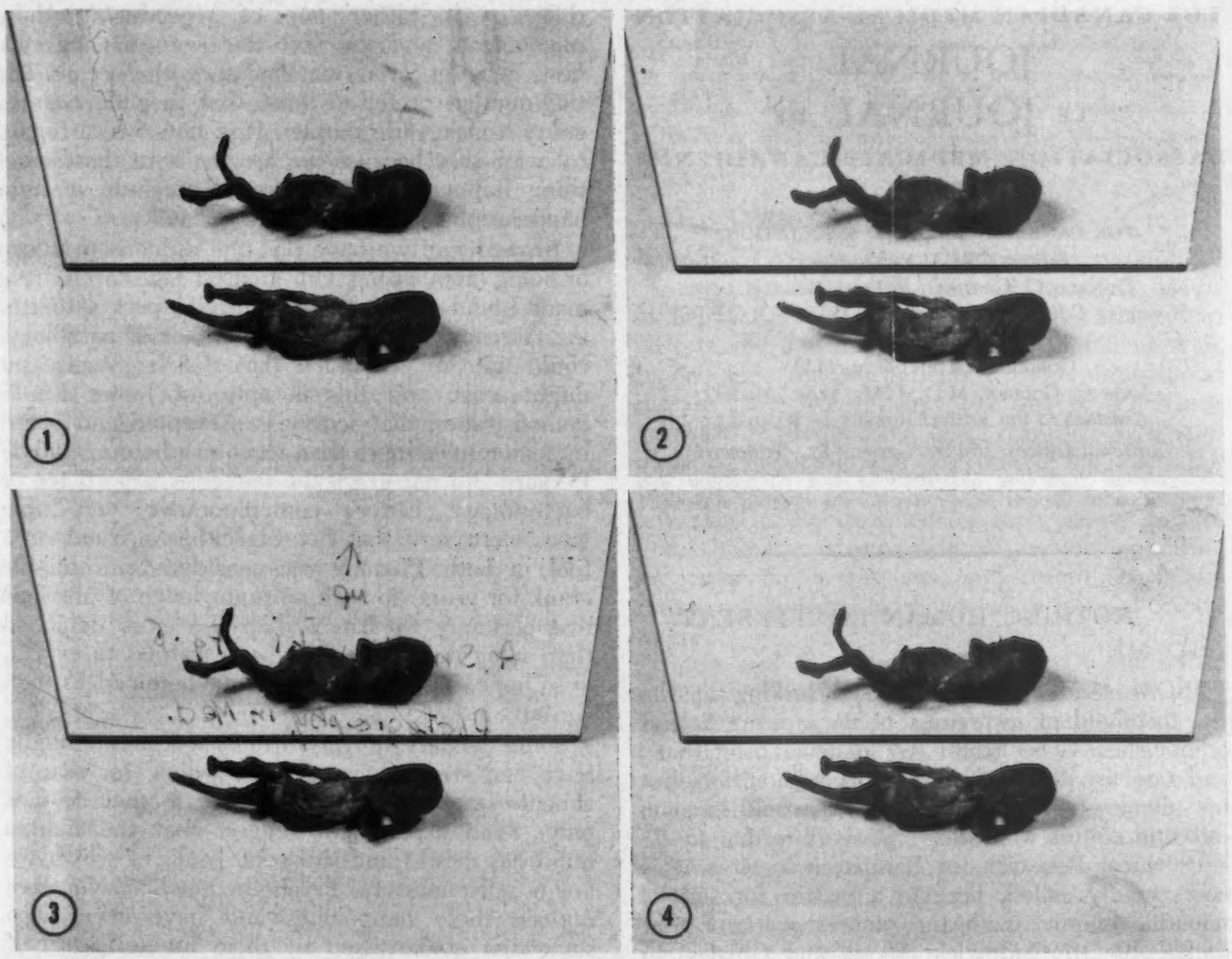

Fig. 7.—Often, photographs are received by the publisher in a damaged condition. Common mistakes include: (1) damage to the print emulsion by a paper clip, (2) crack in the emulsion by rolling or folding photographs, (3) careless marking on the back of a print, defacing an illustration, and (4) fingermarks and cracking from bent corners. If damage occurs, new prints should be made.

turned upwards and the small pieces of tape are removed from the surface of the emulsion side of the print. The outer white margin is trimmed to leave an even white border one-half inch wide.

Grouped photographs should not be permanently mounted on hard cardboard, as it will be difficult to make alterations. For protection the grouped illustration can be lightly tacked at the corners to firm cardboard by tape. Legends must never be written on the reverse side of any photograph to be submitted for publication. Legends are always submitted separately and are referred to by figure number. For identification and orientation, the author's name, figure number, title of the paper or book, an arrow and the word "UP" appear on the reverse side of the illustration.

Well-grouped photographs will greatly increase the teaching value of the illustration. The author should always bear in mind the possibilities of this often forgotten technique of improving illustrations for publication.

PACKAGING AND MAILING

Photographs may be damaged easily by handling and must be adequately protected for shipment to the publisher. Several illustrations can be protected satisfactorily by temporary mounting on firm cardboard. The photograph is attached to an oversized cardboard stiffener by short strips of adhesive tape at the corners. The face of the photograph is protected by a sheet of clean paper. The illustrations are sandwiched between two oversized sheets of corrugated cardboard, and the package is completed by heavy wrapping and cord. The package must be clearly labelled with the correct address of the sender and receiver and should be marked "Photographs, Do Not Bend". The shipment must conform with postal and customs regulations. A large number of illustrations for publication in a book must be well protected by a specially made case of plywood or other hard material.

Poorly protected photographs are often damaged in transit. Illustrations may be torn, creased, punctured or lost if the package falls open. The great care and work expended in making high-quality illustrations warrants careful packaging and shipment to ensure that the illustrations will be received by the publisher in good condition.

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". . . NOTHING HUMAN INDIFFERENT TO ME"

FROM time to time a censor lurking at the threshold of awareness of an aspiring author admonishes: "The Editor would never print that", and one usually gives in to this admonition—but not always—for if one did journals would become dull and editors would have no work to do.

Psychical Research, or Parapsychology as it is now usually called, became a matter for serious scientific enquiry with the pioneer work of that remarkable trio Sidgwick, Myers and Gurney, in Cambridge (England) during the 1880s. It therefore preceded, often by several decades, many branches of science now well established and respectable. In spite of this its place in the assembly of science is a humble one; indeed it is still in danger of being turned away with the quacks, humbugs and charlatans.

This is the more curious if one knows that journals of psychical research have been published for at least three-quarters of a century, and are as dry and uninteresting to the non-specialist as any self-respecting scientific journal should be. Possibly the practitioners of parapsychology are in part to blame for always harping on the incredibility of the phenomena with which they deal. The credibility or otherwise of any particular happening depends upon one's set, one's point of view. Since the 1880s there have been a host of discoveries which would have been incredible then. To pick a few at random, the automobile, radioactivity, subatomic physics, radio, the aeroplane, vitamins, antibiotics, space travel—have all been taken in our stride. Are we really unwilling or unable to admit that we do not necessarily know all that there is to be known about perception, communication, inspiration and that strangest of all things the human mind? One doubts whether it is the incredibility of parapsychology which upsets people; indeed one suspects that many believe in it. The difficulty is rather one of reproducing these phenomena, and the fact that we can't be sure how, why or even whether they do occur. The tidy-minded prefer to think that they do not because it makes life simpler. It is, however, arrogant to insist that because we are not sure that something happens then this must preclude it from happening.

In medicine we have had the dubious privilege of being often wrong. Our greatest sages even, have made blunders which seem, in retrospect, astonishing. Virchow, for instance, the father of pathology, could not be persuaded that deficiency diseases might exist, and this in spite of James Lind's demonstration that scurvy is prevented and cured by lemon juice more than a century before. Claude Bernard did not grasp the immense importance of bacteriology. Lister's contemporaries, very able men, were sure that he was either a fraud or a fool, or both. Fleming was considered an amiable crank for years. So with our knowledge of previous over-certainty we can perhaps be more detached than some disciplines. We have learned to expect, even hope, that time will produce better ideas than we have now.

Some readers of this article will undoubtedly have had strange experiences, which, for fear of ridicule or disbelief, they confide to their friends only. Such experiences suggest that the human mind has depths and shrouded peaks of which we are usually unaware. Psychotherapists[2] have often noticed these happenings and have even been somewhat embarrassed by them for at least half a century, but the serious enquirer will echo the battle cry of that great Chicago physiologist A. J. Carlson, which made him the terror of the unwary, "Vel, and vat is ze evidence?" There are now a number of unusually good books[3-5, 9, 10] devoted to surveys of parapsychology. The best of these, for those who want evidence presented concisely and clearly, is Gardner Murphy's[6] "The Challenge of Psychical Research". He is an ex-president of the American Psychological Association, Director of Research at the Menninger Foundation, and one of the most respected psychologists living today. This is a well-planned book. It consists of long extracts from original papers and reports, combined with lucid and intelligent comments by Dr. Murphy. The selection of these extracts is apt, and Dr. Murphy is neither grandiose or defensive. (Much writing on this subject is flawed by such irrelevancies.) The effect of these spontaneous and contrived happenings is impressive, and with unobtrusive skill Dr. Murphy shows that in spite of increasingly rigorous and skilful experimental design the phenomena still occur. Only recently Mr. Henry Comor of the CBC has produced a remarkable collection of spontaneous cases from Canada which closely resemble those reported over the centuries.

It is curious that Dr. Murphy, who is as sophisticated as he is learned, does not draw our attention

vigorously to the heart of the matter, the mystery of normal perception. Parapsychologists should number neurophysiologists, neurologists, neurosurgeons and psychopharmacologists among their allies. Penfield[7] has given us many clues about the brain as a storehouse of images. Sir Russell Brain[1] reminds us that it is still very difficult to imagine how we perceive anything, and indeed advances in neurophysiology seem to be making this harder to understand. He writes, "Thus when we perceive a two-dimensional circle we do so by means of an activity in the brain which is halved, reduplicated, transposed, distorted and three-dimensional. If physiological idealism is to be really physiological, it must admit that its theory of projection breaks down because the circle which is said to be projected from the cerebral cortex never existed there at all."

Sherrington[8] writing a decade ago discussed perception in a striking passage:

"It is not therefore a physiological conjunction in space but a temporal conjunction in 'mental space'. It is not spatial conjunction of cerebral mechanism which combines them. Identity in time and perceptual space suffice. It instances the 'now' as an integrating factor of the finite mind. It is much as though the right and left eye images were seen each by one of two observers and the minds of the two observers were combined to a single mind. It is as though the right eye and left eye perceptions are elaborated singly and then psychically combined to one. The synthesis is a mental one in which the finite mind uses time as a synthesizer. . . . In all this there is no evidence that the mind-brain correlation requires in any of these combinings the brain to provide spatial conjunction of the two component processes. All that is wanted is concurrence in time. . . . It is as if each eye had a separate sensorium of considerable dignity proper to itself, in which mental processes based on that eye were developed up to even full perceptual level. Such would amount physiologically to a visual sub-brain. There would be two such sub-brains, one for the right eye and one for the left. Contemporaneity of action rather than structural union seems to provide their mental collaboration."

To a great neurophysiologist, a famous neurosurgeon and an eminent neurologist the relationship between mind and brain is still obscure. In such a context the findings of parapsychology need not strain our credulity, and, no longer an offence against nature, become pertinent reflections of the infinite strangeness at the core of our being. In medicine we can be particularly open to the unusual—to paraphrase Terence, "I am a physician, I reckon nothing human indifferent to me." H.O.

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THE CAUSE OF STROKES

VASCULAR disease of the nervous system, besides accounting for about 14% of all deaths in England and Wales, causes much incapacity not only in old age but in the prime of life as well. In one series of 200 patients with cerebrovascular disease, 25% were below the age of 50. These vascular accidents have been regarded as unpredictable, inevitable and untreatable, but this fatalistic attitude is giving way in the face of surgical advances in the treatment of such lesions as subdural hematoma, subarachnoid hemorrhage from an aneurysm or angioma, and cerebral ischemia due to narrowing or occlusion of an internal carotid artery.

Successful treatment in this field is more than ordinarily dependent on correct diagnosis. The fallibility of unaided clinical diagnosis was apparent in the experience of a large neurological department in London where 80 consecutive cases of strokes were investigated by arteriography. In 11 patients in whom occlusion of the internal carotid had been diagnosed, the presence of this lesion was confirmed in four, and such occlusions were found in 10 further cases in which this diagnosis had not been made clinically. Occlusion of the middle cerebral artery was diagnosed clinically in 37 patients but confirmed in only two; of the remaining 35 patients, six were shown to have occlusion of the internal carotid artery, two had intracerebral hemorrhage, and the angiogram was within normal limits in 27.

Carotid arteriography, despite its imprecision, is a valuable aid in detecting extracerebral lesions with considerable accuracy. However, arterial occlusion can be diagnosed with certainty only when it involves large vessels, and often intracerebral hemorrhages cannot be recognized by this procedure. A single angiogram is negative in 60% of strokes and is a procedure that carries a definite risk. In autopsy studies in cases where death has been attributed to cerebrovascular disease, stenosis is commonly observed in the vertebral arteries as well as the internal carotids.

In one recently reported study, Dickinson and Thomson[1] found a close correlation between the blood pressure and the *reduction* in the fluid-carrying capacity of the carotid and vertebral arteries: the higher the blood pressure, the lower was the capacity of these arteries. The lowest capacities of all were found in patients with strokes. These workers found no difference between cases of cerebral hemorrhage and cerebral infarction and concluded that both conditions develop on a similar background of cerebral ischemia.

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Low-Beer and Phear[2] have shown that cerebral infarction, like cerebral hemorrhage, is associated with hypertension. In their study of 109 cases of cerebral infarction, proved at autopsy, the mean blood pressure before the stroke was in the region of 200/110 mm. Hg, and in two-thirds of these cases the blood pressure did not fall at the time of the stroke.

The factors predisposing to either of these accidents, on the same background of cerebral ischemia, are unknown, but acute lowering of the blood pressure does predispose to infarction. This type of lesion commonly occurs during sleep when the blood pressure is at its lowest.

A leading article in a recent issue of *Lancet*[3] draws attention to the extracerebral rather than the intracerebral arteries and to the entire cerebral circulation rather than the artery supplying the affected part. There is no direct correlation between the site of the lesion and the artery in the neck in which the greatest degree of narrowing exists. This suggests that the circle of Willis usually remains an effective anastomosis even when advanced arterial disease is present. Such disease is usually greatest at the origin of the internal carotid and the vertebral arteries and is due to narrowing by atheroma, with the occasional superimposition of old or recent thrombosis. Surgical reconstructive therapy in such cases is directed to the improvement of the blood flow through the circle of Willis, and where both the carotid and vertebral arteries are stenosed, a good clinical result may follow correction of the carotid obstruction. However, surgical therapy rarely dispels established symptoms, and results are best in patients with transient and intermittent symptoms.

REFERENCES

1. DICKINSON, C. J. AND THOMSON, A. D.: *Clin. Sc.*, 19: 513, 1960.
2. LOW-BEER, T. AND PHEAR, D.: *Lancet*, 1: 1303, 1961.
3. Leading Article: *Ibid.*, 1: 1329, 1961.

THE TEEN-AGE DRIVER AND TRAFFIC SAFETY

THE serious hazard posed by the mounting toll of traffic accidents is a direct concern of the medical profession in Canada. This problem is under intensive study by Committees on the Medical Aspects of Traffic Accidents appointed by The Canadian Medical Association and several of its Divisions. The interest of organized medicine in this field is evidenced by the continuous activity of these committees and by a steady flow of recent publications on this subject.

Available statistics indicate impressively that drivers in their teens and early twenties constitute a vulnerable age group that is particularly prone to involvement in traffic accidents. Intensive efforts are being concentrated toward the improvement of driver safety among members of this age group in many centres throughout the North American continent. One of the many avenues of approach in this campaign involves the education of young and recently licensed drivers particularly from the viewpoint of attitudes, motivation, courtesy to others on the road, and plain common sense.

In this regard a recent contribution offered as a public service by the Metropolitan Life Insurance Company in the form of a slim, 15-page booklet entitled "How To Be a Better Teen-Age Driver", is worthy of note.

Copies of this pamphlet may be obtained free of charge from agents or district offices of the Metropolitan Life Insurance Company or from the Company's Canadian Head Office at 180 Wellington Street, Ottawa, Ontario. Educationalists, government bodies, traffic officials and other groups who are now engaged in active programs in the area of driver training may find this publication of value in their efforts to indoctrinate the fundamental principles of traffic safety and courtesy in Canada's drivers of tomorrow.

SEAT BELTS AND TRAFFIC ACCIDENTS

The Canadian Highway Safety Council has recently launched a campaign to encourage the installation and use of seat belts in all motor vehicles.

It is no doubt quite obvious to the medical profession in Canada why such a program should be introduced. During the report of the C.M.A.'s Committee on the Medical Aspects of Traffic Accidents, at our 94th Annual Meeting last June, those of us present were shocked to hear that in 1960 there were a quarter of a million accidents on Canadian highways. This statement was more startling when it was revealed that over 3000 people were killed, and 90,000 were injured.

Medical interest in combating this serious health problem should be accelerated to an even greater degree than it is at the present time. As a member of the Canadian Highway Safety Council, The Canadian Medical Association fully endorses their current drive to encourage the use of seat belts. As individuals we too have an excellent opportunity to support the C.H.S.C. in their worthwhile effort to save lives.

It is my firm belief that the use of seat belts by all occupants of motor vehicles will substantially reduce loss of life and injury.

G. W. HALPENNY, M.D., *President, The Canadian Medical Association*

Letters to the Journal

WHAT IS A PROFESSION?

To the Editor:

Dr. Klass's interesting and charming address, "What is a Profession?", in the September 16 issue (*Canad. M. A. J.*, 85: 698, 1961) has affinities with the always stimulating remarks of Dr. Scarlett in the *Alberta Medical Bulletin*, Autumn 1961, which also refer to the three learned professions of theology, law, and medicine.

May I, however, be permitted a small quarrel with his outline of the historical development of the university as restricted to training for these three professions, training for the teaching profession being left out. My recollections of the "preliminary liberal arts education", reinforced by consulting the Encyclopaedia Britannica to which Dr. Klass does not refer, are that the universities grew out of the studia generalia for the very purpose of training the teacher, the Magister in Artibus, which in those days (I refer to the medieval universities) was a very high degree indeed. It designated the qualification of its holder to teach—largely scholastic philosophy and classics (chiefly Latin plus Aristotle), but later with the opening up of new vistas in the Renaissance, Greek letters and philosophy. They were a pretty tightly organized guild, too, these privileges being pretty well restricted to holders of the M.A. It is true that this applied to university teachers—primary education (except for court and knightly pursuits) was largely in the hands of the church, one of the university-trained "learned professions". There was heavy emphasis on the disciplines of logic, etc., and even after secularization this influence continued to be felt, with clergy prominent in education. The deplorable effects are evident in the "Teachers' Colleges", particularly in the U.S., with their emphasis on "pedagoguery" (even more than pedagogy, like demagoguery), heavily biased in favour of a particular narrow philosophical foundation at the expense of education. Let us hope that the influence of the university will be to restore the tradition of the liberal arts education of teachers, who no more than doctors can in the long run be benefited by too narrow a technical professional training, and who may then rejoin the "learned professions".

W. J. DOWNS, M.D.
Aberhart Memorial Sanatorium,
Edmonton, Alta.

PRIMARY PERITONEAL IMPLANTATION OF AN OVUM

To the Editor:

In 1924 while in general practice, I was called five miles into the country to see an acutely ill 40-year-old married white woman with two teen-age children. She presented obvious signs and symptoms of an ectopic pregnancy. After calling a senior surgeon to meet me at the hospital, I moved her there for surgery. On opening the abdomen a six-weeks' fetus was found implanted on the posterior surface of the uterus. The uterus was enlarged to appropriate size to accommodate the attached placenta which, when dissected off, left the posterior aspect of the uterus presenting an oozing tissue, pitted from placental villi, but without evidence of fistula. The tubes and ovaries appeared normal. The abdomen was packed and closed—leaving drainage. The patient came through the operation satisfactorily, but her condition gradually deteriorated. She presented a typical picture of internal hemorrhage and did not recover.

I have always felt that my father, or other surgeons accustomed to making emergency decisions, would have removed the uterus with the fetus *in situ* and probably saved the patient's life.

Dr. Miller is to be congratulated on the reporting of his case and on his coverage of the literature (*Canad. M. A. J.*, 85: 755, 1961). In 1924 I could find nothing on the subject.

IRLMA KENNEDY JACKSON, M.D.
Postal Station D, Box 240,
587 Concession Street,
Hamilton, Ontario.

MEDICAL NEWS IN BRIEF

THE PREVENTION OF TYPE-SPECIFIC IMMUNITY TO STREPTOCOCCAL INFECTIONS DUE TO THE THERAPEUTIC USE OF PENICILLIN

In a large number of children suffering from β-hemolytic streptococcal infections treated with penicillin, second attacks due to the same specific type of Group A Streptococcus have been observed by Breese, Disney and Talpey (*A.M.A. Am. J. Dis. Child.*, 100: 353, 1960). This indicates that a type-specific immunity has not developed in these children, presumably owing to the therapeutic use of penicillin. Despite this interference with the immune processes, epidemiologic evidence, based on the age distribution of cases over an 11-year period of observation, indicates that the childhood population is developing immunity to the Streptococcus. Therefore fears that the use of penicillin may lead to the development of a non-immune adult population seem without foundation.

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ENZYMATIC IMPAIRMENT OF HEMOSTASIS IN THE URINARY TRACT

Urokinase, an activator of the plasminogen-plasmin system, is normally present in urine, and confers upon it the ability to lyse fibrin clots. Though the source of urokinase is still an unsettled question, it has been suggested that urokinase may play a role in maintaining the patency of the urinary tract by lysing fibrinous deposits. Since such an action might also serve to impair hemostasis in the urinary tract, an investigation was undertaken by McNichol *et al.* (*J. Lab. & Clin. Med.*, 58: 34, 1961) to determine the effect of inhibiting urinary urokinase activity on the duration and extent of the bleeding observed following prostatectomy. Such a study was made possible by the availability of e-aminocaproic acid (EACA), a potent inhibitor of urokinase activity, which, when administered intravenously in appropriate dosage, was promptly excreted into the urine in concentrations sufficient to inhibit urokinase activity.

The daily and total blood losses after transurethral prostatectomy in 12 patients treated with EACA are compared with the results obtained in 15 control subjects. EACA treatment caused a marked reduction in postoperative hematuria, particularly on the first and second days.

A small group of patients were also studied after suprapubic prostatectomy. It was found that, in association with the inhibition of urokinase activity by this acid, there was a significant (fourfold) reduction in blood loss in EACA treated patients as compared with the reduction obtained with control subjects. Levels of this acid in the urine were measured, and the excretion rates and relationship between its concentration and urokinase inhibition are discussed.

The experimental results provide evidence to support the concept that urokinase can impair hemostasis in the urinary tract and that its inhibition may be attended with improved hemostasis.

EXPERIMENTAL TUBERCULOSILICOSIS

Tuberculin-positive guinea pigs were divided into groups and were injected intratracheally with certain pathogenic agents or combinations of agents, especially iron-coated quartz dust plus dead tubercle bacilli, and iron-coated quartz dust plus tuberculin. An extensive pulmonary consolidation was produced by the iron-coated quartz dust in conjunction with dead tubercle bacilli. This consolidation consisted basically of a chronic interstitial pneumonitis with extensive obliteration of air spaces, collagenous fibrosis, focal necrosis, calcification and cavitation. The same dust in conjunction with tuberculin produced a similar consolidation, although there was less collagenous fibrosis, less focal fibrosis, virtually no calcification, and no cavitation.

Gross, Westrick and McNerney (*Am. Rev. Resp. Dis.*, 83: 510, 1961) state that the pulmonary diseases produced by the combination of iron-coated dust with either living tubercle bacilli, dead tubercle bacilli, or merely tuberculin are very similar and differ from one another in minor detail only. The ability of dead tubercle bacilli and of tuberculin, in conjunction with iron-coated quartz dust, to produce pulmonary disease simulating tuberculosilicosis is interpreted to support the thesis that tuberculosilicosis is basically a reciprocal potentiation of the inflammatory response to quartz dust and to the tuberculous infection.

SOME FINDINGS IN ACUTE PORPHYRIA

A study was undertaken recently at the Mayo Clinic to investigate the pathological findings associated with acute porphyria. Nine patients, all male, who were adjudged clinically and biochemically to have had acute porphyria were studied by Ten Eyck, Martin and Kernohan (*Proc. Staff Meet. Mayo Clin.*, 36: 409, 1961). Barbiturates had been administered to eight of them. A family history of porphyria was likely in one and possible in two. Seven had associated potentially fatal disorders.

Abdominal pain, which occurred in five of these patients, is a prominent manifestation of acute porphyria. The pain is frequently severe and may be localized or generalized; there may be associated nausea, vomiting and obstinate constipation. Jaundice is rare; in two patients who had jaundice, other diseases could have been responsible for the finding.

Neurologic manifestations vary from motor weakness to flaccid paralysis. Paralysis was noted in four of the nine cases. Although paresthesia occurred in one case, it may have reflected periarteritis nodosa. Areflexia may occur, but objective sensory changes are rare. Convulsions, occurring in three of these patients, and visual disturbances, which also occurred in three patients, are not uncommon. A hoarse, whispered voice was described in another case. Bulbar involvement with respiratory dysfunction occurred in three of the patients. Rarely is the pressure or protein content of the cerebrospinal fluid increased, as in two cases in this series. Mental changes are frequent, as exemplified in three cases. Hypertension and tachycardia, which were noted in half of these cases, also characterize acute exacerbations. Fever may occur but, like leukocytosis, it may reflect complications.

Although the urine in porphyria frequently is discoloured, freshly voided urine may be colourless. Acute porphyria is characterized by the urinary excretion of delta-aminolevulinic acid, porphobilinogen, Waldenström's uroporphyrin, and increased amounts of coproporphyrin, especially type III. Delta-aminolevulinic acid is a precursor of porphobilinogen, and detection of either compound is highly suggestive of porphyria. Urinary uroporphyrin normally occurs in amounts of 5 to 20 μg. per 24 hr.; however, except in heavy-metal intoxication, its detection by qualitative methods suggests porphyria. Coproporphyrin normally occurs in the urine (100 to 300 μg. per 24 hr.) and feces (300 to 1100 μg. per 24 hr.); it is increased in conditions other than porphyria.

Barbiturates have long been thought to cause exacerbations of acute porphyria; such a history was obtained in eight of the nine patients. In two patients exacerbation followed operations during which thiopental anesthesia had been used. The incidence of acute porphyria is greater in women; it is striking that all nine patients in this study were men. As is true of hypertension and pyelonephritis, acute porphyria may be more lethal in men, although its incidence in women is greater. A family history of porphyria was established in one case and was probable in two others.

Hepatic changes occurred in most cases and included congestion, centrolobular necrosis, and fatty degeneration; granules of iron-free lipochrome pigment were found in the hepatic cells of half of the patients. Pulmonary infarction had occurred in three cases. Neu-

rogenic atrophy of the muscles with hyaline degeneration was present in almost half of the patients. Atrophy of the testes had occurred in all the patients who had symptomatic acute porphyria at the time of death.

Neuropathologic changes were found in the eight cases in which nerve tissue was available. Patchy demyelination and degeneration of the axis cylinders were present in the peripheral nerves, dorsal roots, cauda equina, and autonomic nervous system. Degeneration of nerve cells was found in the anterior-horn cells of the spinal cord, dorsal-root ganglia, cerebellum, dorsal nucleus of the vagus nerve, and the celiac plexus. Minor, nonspecific alterations were present in the cerebral cortex of half the patients who were free from associated diseases.

(Continued on advertising page 34)

ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

INVITATION TO CERTIFICATED SPECIALISTS OF THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA TO ATTEND THE 1962 ANNUAL MEETING OF THE COLLEGE

In 1959, the College, in keeping with a policy of expanded educational opportunities for Fellows and certificated specialists, embarked on a program of Regional Scientific Meetings, which Fellows and certificated specialists living in the designated region have been invited to attend.

At the 1961 Annual Meeting of the College held in Ottawa, certificated specialists in the immediate local area were invited to attend the scientific program sessions.

Because of the larger meeting-room accommodation available in Toronto, the Council of the College has decided to extend an invitation to all certificated specialists of The Royal College to attend the scientific sessions at the 1962 Annual Meeting, to be held at the Royal York Hotel, Toronto, from January 18 to 20.

Certificated specialists wishing to attend this meeting must complete the attached registration application form and return it to The Secretary, The Royal College of Physicians and Surgeons of Canada, 74 Stanley Avenue, Ottawa 2, Ontario, together with a cheque or money order in payment of the Registration Fee of $15.00, made payable to the Royal College of Physicians and Surgeons of Canada. In order to facilitate planning for adequate accommodation, registration applications should be forwarded by December 15 at the latest.

A summary of the scientific program will be published in the Journal in mid-December. Certificated specialists who have registered to attend the meeting will also be sent a copy of the printed program at that time.

The Secretary,
The Royal College of Physicians and Surgeons of Canada,
74 Stanley Avenue,
Ottawa 2, Ontario.

I desire to register to attend the Scientific Sessions of the Annual Meeting of The Royal College of Physicians and Surgeons of Canada to be held at the Royal York Hotel, Toronto, January 18, 19 and 20, 1962.

Enclosed is a cheque/money order in the amount of $15.00 in payment of the Registration Fee.

Name of Certificant:.....

Address:.....

.....

Name of Specialty:.....
(please print)

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ASSOCIATION NOTES

SUMMARY AND RECOMMENDATIONS OF THE BRIEF TO THE ROYAL COMMISSION ON HEALTH SERVICES FROM THE MEDICAL SOCIETY OF NOVA SCOTIA

1. Our studies in preparing this brief have impressed on us the extent and multiplicity of the health services which are available in the interests of the patient as an individual and the public as a whole.
2. This section is based on ". . . recommending methods of ensuring that the best possible health services be available to all Canadians". We believe that, in the provision of medical services in prevention, diagnosis, treatment and rehabilitation, the physician has been and will be the central factor.
3. Our recommendations relate themselves to our proposals for priorities in the improvement of health services (Term [k], Page 94). We emphasize, however, that attention to any one element should not be so intense that other essential features are disregarded. In our view improvements should be proceeded with on a broad front. We recognize that neither public nor private financing will permit implementation of all the desirable extensions of health services at one time to their fullest extent. With these considerations in mind we submit the following recommendations.

4. RECOMMENDATION 1

The Training of Health Personnel

Deficiencies in the number of physicians available to serve the needs of the people of Nova Scotia have been disclosed in our studies. We are dependent in large measure on the graduates of the Faculty of Medicine of Dalhousie University for the general practitioners and specialists who practise in this Province. Our first recommendadion therefore relates itself to aid to medical education and we propose a capital investment of $4.5M. of public and private funds to provide for the expansion of the Dalhousie Medical School. Details of the proposal are outlined in the narrative portion of our submission relative to Terms [e] Page 67, [f] Page 71, and [g] Page 78.

5. The recruitment of medical students must be accelerated. In all its studies and recommendations it is our hope that this Commission will keep in mind that a career in medicine should be made more attractive by reason of any changes proposed.
6. The maintenance of adequate facilities for medical education will involve an annual sum of unknown but substantial amount. The support of the only medical school in the Atlantic provinces is worthy of increased financial participation of the four provinces concerned, as well as that of the Federal authority. Grants to medical undergraduates will be necessary to permit them to finance the long, expensive course and to ensure sufficient recruitment of suitable medical students.
7. Not less urgent is the need for increased numbers of paramedical workers of all types. In certain instances, training facilities in the Atlantic provinces will require enlargement and support. In other cases where no facilities exist, the establishment of schools and courses is necessary. On Page 13 (Paras. 43-60), we have outlined the deficiencies as we see them and we recommend the amplification of the Professional Training Grant under the National Health Grants program to assist the training of these essential workers.
8. Closely related to the education and training of health workers is medical research and it is evident that the pursuit of new knowledge and better methods is fundamental to the improvement of health services. It is our view that funds for research should be provided largely through continued and increasing support of the Medical Research Council. However, it will be impossible and undesirable to separate completely clinical investigation from medical services or hospital insurance programs. (See Term [j], Page 92.)

9. RECOMMENDATION 2

The Provision of Physical Facilities for Improved Health Services

Although we have designated the provision of trained personnel as our primary requirement, concurrent action in the provision of physical facilities must go forward. In our appraisal of the situation under Term [f], Page 71, we have stated that active and long-term treatment hospitals to a level of 6.9 beds per 1000 of our population is a valid objective. We recommend that the construction of 1170 additional active treatment beds be proceeded with and we estimate the capital cost of construction to be approximately $23.4M.

10. The construction of 920 beds for the care of convalescent, chronic and terminal patients, preferably located in close relationship to active treatment hospitals, is also necessary. We estimate the construction cost of these facilities to be $9.2M.
11. We further recommend that a rehabilitation centre be constructed at an approximate cost of $3M., that community health centres be provided in areas of need, that facilities for mental health clinics be considerably amplified and that a hostel for the accommodation of patients attending the Nova Scotia Tumour Clinic be constructed. We estimate the capital cost of the latter three facilities to be of the order of $350,000.
12. The implementation of our recommendation for the reform of the mental health services will unquestionably require the replacement of facilities but we are not at this time prepared to estimate the cost involved.
13. We fully appreciate that expenditures of considerable magnitude will be required to bring our present health facilities up to a reasonable standard

of adequacy and that their maintenance will involve substantial annual outlays.

14. Our thoughts on methods of financing are outlined in the comment under Term of Reference [i], Page 80.

15. RECOMMENDATION 3

Universally Available Voluntary Medical Services Insurance

We have spelled out in considerable detail our belief that comprehensive medical services insurance should be available to every resident of Nova Scotia regardless of age, state of health or financial status (Page 39, Para. 140; Page 63, Para. 210).

16. We recommend that for 100,000 of our fellow citizens who may be classified as indigent, the total cost of such services be paid from public funds. For those above this level of economic status, who can prove need, we suggest that assistance be provided to enable them to purchase the coverage which they require. For the self-supporting majority, we recommend that they be encouraged to continue to be responsible for personal health services by insurance coverage or from their own resources (Pp. 90-91).

17. We recommend that one or more approved carriers of medical services insurance be identified and that the plan be subsidized to the degree required to provide service to the groups already mentioned and to permit the enrolment of individuals of any age or state of health.

18. We have estimated that the cost of providing comprehensive medical insurance coverage to the "medically indigent" would be $2.5M. per year.

19. No estimate has been made of the cost of subsidizing those who require partial assistance or the extra cost of enrolling those over 65.

20. RECOMMENDATION 4

Reform of the Programs on Mental Health Services, Rehabilitation and Cancer Control

At Paragraphs 104-112, Page 27, we have commented on the services available to the population in the field of mental health, and many deficiencies have been pointed out. In our view, there is urgent need for a new approach to the problems of mental ill-health, particularly with respect to institutional services.

21. Twelve recommendations are presented which are designed to accomplish the necessary reform (Page 32, Para. 128). It has not been possible to estimate the cost of the improvements which we propose but they will undoubtedly involve a considerable outlay of public funds.

22. The rehabilitation of the sick and injured may be regarded as a neglected area of health services and the facilities available in Nova Scotia represent nothing more than a beginning. We have discussed the essentials of an adequate service and have incorporated several recommendations to achieve it (Page 39, Para 141; Page 40, Para 143). Aside from a recommended expansion of the facilities of the Nova Scotia Rehabilitation Centre at an estimated cost of $3M., we have not undertaken to project the expenditures necessary to provide adequate rehabilitation services throughout the Province.

23. Through the operation of the Nova Scotia Tumour Clinic an impressive start has been made in the diagnosis of cancer and its treatment by radiotherapy and surgery. Improvements in the service of cancer control and its extension throughout the Province are discussed on Page 34, Paras. 138-145, and we recommend as an initial step the establishment of a hostel for the accommodation of patients attending the Nova Scotia Tumour Clinic to spare the use of active treatment beds. An expenditure of $100,000 for this purpose would in the long run prove economical.

24. RECOMMENDATION 5

Public Health

The foregoing recommendations each have a bearing on the public health. The Department of Public Health of Nova Scotia is an integral component in the provision of health services. There are areas of health care which require a co-ordinated approach by the Department of Public Health, the medical profession and other interested bodies. We recommend that the following be considered in this context: cardiorenal disease, traffic accidents, rheumatic diseases, maternal and perinatal health, child health, health of the aged and alcoholism.

25. RECOMMENDATION 6

Miscellaneous Improvements

In our appraisal of the health services currently available in Nova Scotia, we have encountered situations where improvements should be instituted without fundamental change in the character of the service itself. In this category we recommend:

(a) the better identification of eligible patients under the Indian Health Services and the promulgation of a more realistic schedule of medical fees.

(b) the institution of freedom of choice of doctor by entitled Sick Mariners in place of the Port Physician system.

(c) the extension of the current public program for the provision of drugs to the chronically ill, to include patients who are not under institutional care, including the mentally ill, the patients under the cancer programs and those who are being rehabilitated.

(d) that the beneficiaries under the Federal Civil Servants Group Surgical Medical Insurance Plan be afforded a choice of carrier. If groups decide that the service benefits available under plans such as Maritime Medical Care are preferable, then the employer's contribution and the privilege of payroll deduction should be applicable (Page 23, Para. 93).

26. Finally, Mr. Chairman, we wish to express to you and the Commissioners our full appreciation of the magnitude and importance of the task which, as a Royal Commission, you have undertaken. In the time available since the announcement of your terms of reference we have as-

siduously applied ourselves to a study of each item, resulting in the foregoing recommendations and the narrative which follows. The results of certain studies already initiated will be made available to you as soon as possible.

27. The Medical Society of Nova Scotia wishes you well in your inquiries and the formation of your recommendations and is prepared to offer your Commission any assistance of which we are capable.

PUBLIC HEALTH

SUMMARY OF REPORTED CASES OF NOTIFIABLE DISEASES IN CANADA*
ISSUED BY THE PUBLIC HEALTH SECTION, DOMINION BUREAU OF STATISTICS

Disease	*Week ended (1961):* August 19	August 26	Sept. 2	Sept. 9	*Cumulative total since beginning of year* 1961	1960
Brucellosis (Undulant fever) (044)	1	2	3	7	89	104
Diarrhea of the newborn, epidemic (764)	—	3	3	1	66	37
Diphtheria (055)	3	1	1	4	52	22
Dysentery (045, 046, 048)	105	64	100	108	2,365	1,971
(a) Amebic (046)	1	—	—	—	6	2
(b) Bacillary (045)	37	30	35	52	1,069	1,689
(c) Other and unspecified (048)	67	34	65	56	1,290	280
Encephalitis, infectious (082.0)	—	—	2	—	3	4
Food poisoning: (049.0, 042.1, 049.2)	23	22	24	93	841	942
(a) Staphylococcus intoxication (049.0)	—	3	—	—	24	309
(b) Salmonella with food as vehicle of infection (042.1)	22	19	24	23	718	607
(c) Unspecified (049.2)	1	—	—	70	99	26
Hepatitis, infectious (including serum hepatitis) (902, N998.5)	231	133	214	194	7,341	3,853
Meningitis, viral or aseptic (080.2, 082.1)	16	19	15	18	204	485
(a) Due to poliovirus	5	8	2	2	32	246
(b) Due to Coxsackie virus	1	1	—	1	12	101
(c) Due to ECHO virus	—	—	—	—	—	7
(d) Other and unspecified	10	10	13	15	160	131
Meningococcal infections (057)	4	2	1	—	86	122
Pemphigus neonatorum (Impetigo of the newborn) (766)	—	—	—	—	9	7
Pertussis (Whooping cough) (056)	118	106	88	118	2,941	3,872
Poliomyelitis, paralytic (080.0, 080.1)	10	20	6	7	105	608
Scarlet fever and Streptococcal sore throat (050, 051)	127	76	102	127	9,706	16,930
Typhoid and Paratyphoid fever (040, 041)	2	4	9	8	182	245
Venereal diseases (020-038)‡	455	350	443	372	12,608	12,006
(a) Gonorrhea (030-034)	396	294	386	328	11,035	10,612
(b) Syphilis (020-021.3, 023, 024, 026-029)	59	56	57	44	1,572	1,391
(c) Other† (036-038)	—	—	—	—	1	3

*Figures for the Yukon are received four-weekly and are, therefore, shown in the cumulative totals only.
†Including chancroid, granuloma inguinale and lymphogranuloma venereum.
‡Excluding 021.4, 022, 025 and 035.

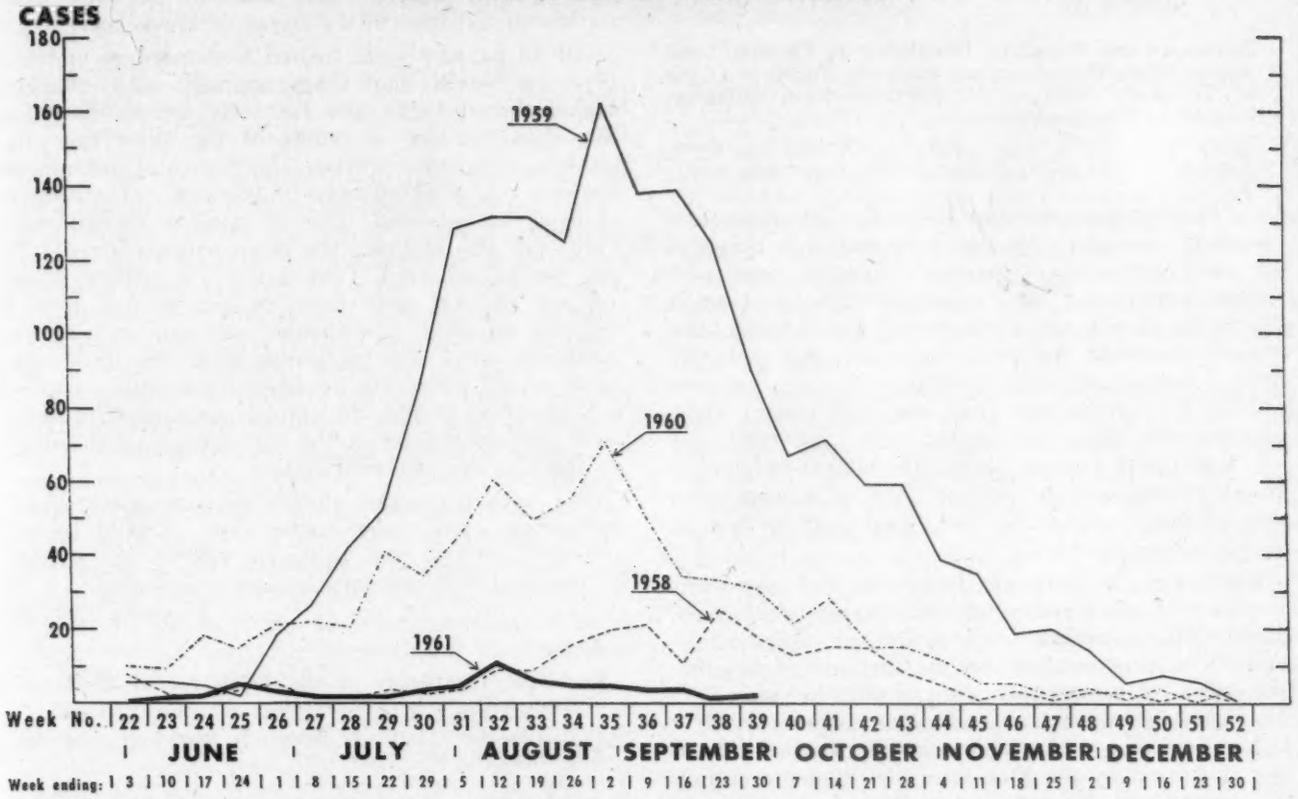
PARALYTIC POLIOMYELITIS IN CANADA*
39TH WEEK—ENDING SEPTEMBER 30, 1961

	Reported cases									*Deaths*		
	This week			*Last week*			*To this date*			*To this date*		
	1961	1960	1959	1961	1960	1959	1961	1960	1959	1961	1960	1959
Canada	2	32	91	1	34	126	126	783	1455	6	68	136
Newfoundland	—	1	5	—	1	9	10	42	124	—	4	8
Prince Edward Island	—	—	—	—	—	1	—	—	4	—	—	—
Nova Scotia	—	—	2	—	—	1	1	9	6	1	1	—
New Brunswick	—	4	6	—	4	3	1	80	37	—	2	5
Quebec	—	17	45	—	15	70	60†	249	966	3	30	88
Ontario	—	—	14	1	2	22	18†	27	156	—	1	16
Manitoba	—	—	1	—	1	1	—	10	25	—	1	2
Saskatchewan	2	2	2	—	1	4	7	51	33	—	8	3
Alberta	—	7	3	—	9	3	25	161	39	2	9	3
British Columbia	—	1	13	—	1	12	4	154	54	—	12	7
Yukon	—	—	—	—	—	—	—	—	—	—	—	—
Northwest Territories	—	—	—	—	—	—	—	—	11	—	—	4

*Weekly returns based on telegraphic reports by provinces.
†Includes two new delayed reports.

Epidemiology Division, Department of National Health and Welfare, Ottawa, October 5, 1961

**PARALYTIC POLIOMYELITIS; REPORTED WEEKLY INCIDENCE
1961 AND SPECIFIED YEARS — CANADA**



OBITUARIES

DR. E. STANLEY BRIDGES, 73, died at his home in Ottawa on August 30, 1961.

Born in Fredericton, N.B., Dr. Bridges was a graduate of the University of New Brunswick in 1908 and a winner of the alumni gold medal and the Lieutenant-Governor's prize for the best all-round scholar. He practised medicine for 20 years in Saint John, N.B.

Dr. Bridges is survived by his widow.

Le DR LEOPOLD CARIGAN, âgé de 74 ans, est décédé à Beauharnois, le 10 septembre 1961.

Né à St-Pierre les Becquets, le Dr Carigan fit ses études au Séminaire à Trois-Rivières, Québec. Il obtint son degré en médecine à l'Université de Montréal en 1911.

Il laisse dans le deuil trois fils et deux filles.

DR. RALPH B. COX, 84, a Connecticut physician, died on September 12, 1961, at his summer residence in Kingsport, N.S.

Born in Kingsport, N.S., Dr. Cox graduated from Dalhousie University, and in 1902 from McGill University. He had practised medicine in Collinsville, Conn., for 59 years.

He is survived by one daughter.

DR. DAVID ESSER, 71, died on September 10, 1961, in New Mount Sinai Hospital, Toronto, Ont. Born in Vilna, Russia, Dr. Esser came to Toronto as a young man and graduated from the University of Toronto Medical School in 1920. In 1936 he received a degree in ophthalmology from the University of Pennsylvania and worked in this field until his death.

He is survived by two daughters.

DR. WILLIAM T. KERGIN, 85, a St. Catharines' physician who earned the title of "pioneer doctor of northern British Columbia" died recently in Vancouver. After graduating in medicine from the University of Toronto in 1902, and interning at Grace Hospital, Dr. Kergin moved to the West where he was in charge of hospitals—one at Fort Simpson, and the other at Port Essington. He later moved to Prince Rupert, where he practised with his brother.

He is survived by his widow, two sons and a daughter.

DR. GEORGE T. ZUMSTEIN, 64, radiologist at the St. Catharines (Ont.) General Hospital, died at his home on September 10, 1961. Dr. Zumstein was born in Hamilton, Ont., and received his M.D. from the University of Toronto in 1920. He completed his residency at the McGill University Pathological Institute in 1925.

He is survived by two daughters.

Canad. M. A. J.
Nov. 4, 1961, vol. 85

(Continued from advertising page 8)

SURGERY

Pulmonary and Bronchial Circulation in Chronic Lung Apneumatosis. Physiologic and Anatomic Studies in a Case of Traumatic Rupture of the Main-Stem Bronchus Treated by Pneumonectomy.

A. R. VIOLA, O. A. VACCAREZZA, A. V. UGO AND E. B. VISCARDI: *J. Thorac. Cardiovasc. Surg.*, 41: 459, 1961.

In a case of traumatic rupture of the left main-stem bronchus, secondary to closed trauma that occurred 14 years previously, pulmonary function tests performed before and after operation showed common alterations in restrictive pulmonary insufficiency, but without anoxemia. Right-heart catheterization was performed before and after operation. During this procedure, pressure records from the right atrium, right ventricle, the main pulmonary artery, and right and left stems were normal except for the left pulmonary branch in which in the "wedge" position a mean pressure approximately three times higher than that in the trunk was recorded.

Blood samples from all these sites and also from the brachial artery were obtained. Oxygen and carbon dioxide determinations were performed according to Van Slyke manometric technique. In the left pulmonary artery, an oxygen saturation of 96% was found; in the right stem there was an oxygen content 2 vol. % higher than that in the right ventricle. Cardiac output was calculated by the Fick principle. Systemic output was determined by considering the oxygen arterial-venous difference between the arterial sample and that from the right ventricle. Pulmonary output was calculated by considering the arterial-venous difference between the arterial sample and that from the right pulmonary artery. In this way, a left-to-right shunt in the pulmonary circuit was demonstrated and evaluated.

After pneumonectomy, no alterations in pulmonary circulation were found. Pneumonectomy—which appears to be mandatory in such cases—was performed because of lung destruction and to avoid a left-to-right shunt in the pulmonary vascular bed reduced to one-half its previous volume. The gross specimen of the left lung demonstrated the abnormal development of the lung collateral circulation and its anastomosis with the pulmonary system.

S. J. SHANE

THERAPEUTICS

Nitrogen-Mustard Therapy Combined with Autologous Marrow Infusion.

P. CLIFFORD, R. A. CLIFT AND J. K. DUFF: *Lancet*, 1: 687, 1961.

The authors report the results of palliative treatment with large doses of nitrogen-mustard, up to a total of 2 mg. per kg. body weight, in 33 patients with advanced or generalized malignant growths.

In Kenya the incidence of malignant disease of the paranasal sinuses and postnasal space is relatively high. In East Africa radiotherapy is not available and therefore chemotherapy is the only form of treatment for patients with growths unsuitable for surgery. In this series, two classes of case were deemed unsuitable for surgery and were given nitrogen-mustard therapy: (1) those with regional growths beyond the scope of surgery (growths of the postnasal space) and (2) those with generalized tumours. Histologically, the tumours treated in the former class were anaplastic carcinomas or lympho-epitheliomas, and those in the latter were round-cell sarcomas of the upper or lower jaw.

All 33 patients were treated with nitrogen-mustard in doses higher than those normally used, that is, higher than 0.1 mg. per kg. body weight daily for five days, because of failure of the lower doses to produce adequate response. The degree of antitumour response was observed to be proportional to the amount of drug administered. The 15 patients treated with 1 mg. per kg. all lived; the three patients given 1.25 mg. per kg. all lived. Two of the nine patients given 1.5 mg. per kg. died; three patients treated with 2 mg. per kg. died. The deaths were due to infection combined with toxic agranulocytosis. The three patients treated with 2 mg. per kg. and autologous marrow infusion all recovered; the autologous marrow infusions were used to counteract the toxic affects of the drug on the reticuloendothelial system.

The authors suggest that nitrogen-mustard as an antitumour agent, using higher doses, should be reassessed, and that such doses are safe for the patient if combined with autologous marrow infusions.

FRANCES LETTAU

Perfusion Techniques in the Treatment of Malignant Disease with Cytotoxic Agents.

W. T. IRVINE AND C. F. NOON: *J. Roy. Coll. Surgeons Edinburgh*, 6: 205, 1961.

A brief review of the history of methods for the destruction of malignant cells by chemotherapy is presented. In the present series 22 cases were treated. The tumours treated, the type of perfusion and the cytotoxic agent employed in each case are outlined. The drug doses, mode of administration and the factors limiting drug dosage in regional perfusion are discussed. The extra-corporeal circuit and the technique of perfusion are described fully. The effects obtained in some of the patients are presented. The systemic complications encountered were shock, marrow depression, gastrointestinal disturbances and liver damage, and the local complications were edema, skin changes (erythema and blistering), vascular damage and wound sepsis.

Several conclusions were drawn from the results of this series: (1) isolated perfusions allowed much larger amounts of cytotoxic drugs to be administered to peripheral tumours, but the normal tissue tolerance was still a limiting factor; (2) the technique of marrow aspiration and reinfusion following total body perfusion allowed larger doses of these drugs to be administered in diffuse malignant conditions; (3) malignant melanomas appeared regularly to respond to phenylalanine mustard, and it might be that regional perfusion used as an adjuvant to classical treatment will increase the survival rate in early cases; (4) either regional or total perfusion appeared to offer considerable palliation in advanced cases of malignant melanoma; (5) tumours other than melanomas did not show a high incidence of response, but much more information is required about selection of cytotoxic agents for individual tumours. It is possible that combinations of several drugs with different regional side effects and multiple perfusions will enhance the results.

FRANCES LETTAU

BOOK REVIEWS

PRINCIPLES OF MEDICAL STATISTICS. 7th ed. A. Bradford Hill. 367 pp. Illust. The Lancet Limited, London, 1961. 12s. 6d. net.

This is the seventh edition of a fine book which has now reached two editions in Spanish and one each in Russian and Korean. The author has tried to set down as simply as possible the statistical methods that experience has shown him to be the most helpful in the problems with which medical workers are concerned. The work is actually a re-issue in book form of a series of articles on medical statistics published in *The Lancet* in 1937, but now, of course, with many revisions and alterations. Three new chapters have been added to this recent edition, dealing with the elements of sampling, the carrying out of scientific investigations, and the problems of defining and measuring sickness.

There is repetition, but this is of definite value to the beginner, often horrified by equations and square roots. The author himself offers as an excuse the repetition in published papers of those elementary statistical errors which a very little knowledge of statistics would be sufficient to prevent.

This Journal has recognized the importance and the increasing use of statistics, and the student of medical statistics is also referred to a series of articles published earlier this year (*Canad. M. A. J.*, 84: 376, 431, 487, 545 and 591, 1961).

NEWER DIMENSIONS OF PATIENT CARE. Part I. The Use of the Physical and Social Environment of the General Hospital for Therapeutic Purposes. Esther Lucile Brown. 159 pp. Russell Sage Foundation, New York, 1961. $2.00.

As the title suggests, this is the first of three books which will analyze the work of the modern hospital from a psychosocial point of view. It is one of the most stimulating and thought-provoking discussions on the meaning of patient care that the reviewer has seen. We are forcibly reminded that patients are primarily people in trouble. Some of their fears on going to a hospital are defined, fears not only about the unknown surroundings but also about their families, the position of complete dependency in which they now find themselves, and the enforced changes in patterns of living, for example, early meal hours and the question of bathroom privileges. The hospital role of a person is often a drastic change from his role in the family and community.

Dr. Brown goes on to describe the perceptions and expectations of patients in a hospital, the use of familiar objects, such as a clock, calendar, books and other things as measures of comfort. She discusses the importance of how all members of the staff act toward the patient from the very moment of reception, the role of visitors, and the gradual trend to more flexibility in visiting hours, particularly for children. She gives examples of hospitals where parents may stay with their children overnight. This may be important also to older people from other ethnic backgrounds who are unaccustomed to our pattern of hospital care.

One of the most interesting ideas is the role of the patient as a helper in the therapeutic process with other patients. This, of course, has been developed to some extent in progressive patient care units and in rehabilitation units, but so far not in adult acute hospitals. The author points out that patients with backgrounds in nursing or medicine may find themselves in their accustomed surroundings but completely out of the picture for the first time in their lives. This is also true of others who just want to have something to keep them busy and occupied, such as writing letters for someone else, interpreting for foreign patients, and delivering mail.

The book is filled with many interesting direct comments from patients, nurses, doctors, and others, and it raises some fascinating questions in the reader's mind. One begins to realize that with the increasing complexity of modern medicine the hospital has become the laboratory or work place for the hospital staff rather than primarily a place for the care of patients. Many of the real social and emotional needs of patients are being ignored. Little is being done to alter the increasingly rigid and authoritarian basis on which large hospitals, in particular, are run today. This lively and provocative book is most heartily recommended to all doctors, nurses, and others who "think" they are caring for patients.

EXPERT COMMITTEE ON HEALTH STATISTICS. Seventh Report. World Health Organization Technical Report Series No. 218. 28 pp. World Health Organization, Geneva, 1961. $0.30.

The major purpose of this report is to point out the ways in which national and local health administrations may supplement the routine collection of vital statistics by the use of survey techniques. The objectives, types, methodology, possible uses and limitations of morbidity and health surveys are discussed. Surveys may be simple for developing countries which lack trained staff, or they may be quite complex in design for developed countries which are able to process more extensive information. Three main types of survey may be used—the interview survey, the health examination survey, and the survey based on existing records. The value and limitations of each approach are presented. A particular section is devoted to the use of local health surveys and specific disease surveys in less developed areas.

The report goes on to discuss the development of international statistical classification of diseases, injuries, and the causes of death, its extension to more and more countries, and preparations for the eighth revision. Brief references are made to the U.N.-W.H.O. seminar on the use of vital and health statistics for genetic and radiation studies, the need for a bibliography on health survey methods, proposed studies of the better use of hospital statistics, the desirability of setting up national committees on vital and health statistics, and the continuation of a variety of W.H.O.-sponsored studies in the health statistics field. This report will be of special interest to those doing statistical work. The general discussion of survey techniques should be useful to anyone wishing to carry out disease or health surveys.

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THERAPEUTIC EXERCISE. 2nd ed. Edited by Sidney Licht and Ernest W. Johnson. 959 pp. Illust. Elizabeth Licht, Publisher, New York, 1961. $16.00.

The demand for a second edition of this text within three years of the publication of the first edition shows that it fills an essential need. Without doubt a book of this type is a valuable reference work for all medical libraries.

There is an excellent coverage of muscle structure, muscle physiology, the mechanics of posture, and exercises for all types of joints.

The division of the chapters into exercises for various diseases and injuries tends to make for some repetition, but on the other hand it is a great deal easier for reference purposes. This is a text that every physiatrist and physiotherapist should possess. It would be of value also to orthopedic surgeons and neurologists as a reference work.

There is an excellent discussion and summary of the uses of orthoptic training, which should enable the physician to answer questions frequently posed by patients.

The reviewer doubts whether all will agree with the statement that much of the disability in multiple sclerosis follows from disuse. However, the exercises suggested are undoubtedly helpful in this condition.

This second edition contains chapters on isometric exercises and gait retraining which were not offered in the first edition, except in a brief appendix.

MYXEDEMA. Jerry K. Aikawa. 106 pp. Charles C Thomas, Springfield, Ill., 1961. $5.00.

In this little monograph Dr. Aikawa succeeds in capturing the imagination with his account of the development of medical knowledge concerning myxedema. While describing the "rare, brilliant flashes of intuition on the part of some and the dogged determination of others", he has at the same time condensed the vast body of medical knowledge concerning thyroid physiology so that the reader gains a real understanding of this important endocrine organ almost unconsciously.

As well as outlining the history from the time that King described the histology of the thyroid, and Gull first recognized myxedema as a clinical entity, he gives a good account of the effect of thyroid hormone on body tissue, the chemistry of thyroxin, the contribution of radioactive iodine to the study of thyroid disease, and the interrelationship between the thyroid and the pituitary glands.

It can be recommended to medical students and to practitioners wishing a concise review of some of the modern concepts of thyroid function. It will almost certainly, as the author hopes, result in motivating a few students of medicine "to join in the task of solving the many unanswered questions raised".

CONTROL OF SOIL-TRANSMITTED HELMINTHS. World Health Organization Public Papers No. 10. Paul C. Beaver. 44 pp. World Health Organization, Geneva; Columbia University Press, New York, 1961. $0.60. Also published in French.

Among all the species of worms parasitic in man the soil-transmitted intestinal nematodes—the roundworm, the whipworm, and the hookworm—hold the distinction of exerting the greatest influence on individual health and group productivity throughout the world, their prevalence in different communities serving indeed as an index of social and economic standing. Although they cause anemia, reduce physical and mental capacity, weaken resistance to other diseases, and at times affect health directly and severely, attempts at their control have met with disappointing results, and as a consequence they present a health problem that is apt to be given perfunctory attention or even neglected.

Professor Beaver discusses in this new WHO publication the factors involved in the control of these soil-transmitted helminths, the control methods that have been employed and should be employed, and the research problems that programs of control raise. A section is devoted to other miscellaneous helminths whose role in parasitic infections is still somewhat obscure. An annex deals with diagnostic methods.

KLINISCHE CHIRURGIE FUR DIE PRAXIS. In vier Bänden. Band I, Lieferung 5. Edited by O. Diebold, H. Junghanns and L. Zukschwerdt. pp. 937-1087. Illust. Georg Thieme Verlag, Stuttgart, West Germany; Intercontinental Medical Book Corporation, New York, 1961. $9.75.

In this final section of the first volume under the heading of malformations of the head and face, one finds a short and clear presentation on hare-lip, cleft palate and the diverse types of "dysostoses" and other minor or rare deformities. This monograph is a useful summary of borderline diseases belonging partly in the field of orthopedics and in regard to treatment usually requiring the help of a plastic surgeon.

The injuries of soft tissues and bones are the subjects of the second monographs, followed by the presentation on benign and malignant tumours affecting these tissues.

In the last chapter, under the heading of Diseases of the Neck, the "swellings" of this region are thoroughly covered. This is one of the most informative and useful contributions of this volume. The illustrations and references are well chosen, as in the previous sections.

MEDICAL DEPARTMENT, UNITED STATES ARMY. PREVENTIVE MEDICINE IN WORLD WAR II. VOL. V, COMMUNICABLE DISEASES Transmitted Through Contact or by Unknown Means. Edited by Colonel John Boyd Coates, Ebbe Curtis Hoff and Phebe M. Hoff. 530 pp. Illust. Office of the Surgeon General, Department of the Army, Washington, D.C., 1960. $5.75.

A well documented and illustrated account of the problem and means taken to combat communicable diseases in the U.S. Army in World War II. Hepatitis furnished the most unexpected and perhaps the most serious problem of all the diseases discussed in the volume. A perusal of this volume indicates what happens to normal morbidity or sickness when war intervenes. The book would be most valuable if and when a similar situation returns to plague mankind.

MATHEMATICAL PRINCIPLES IN BIOLOGY AND THEIR APPLICATIONS. A Monograph in American Lectures in Living Chemistry. Nicholas Rashevsky. 128 pp. Charles C Thomas, Springfield, Ill., 1961. $6.00.

This is a condensation, in relatively non-technical language, of some of the volumes on biomathematics for which the author is justly celebrated. Reading it is a

(Continued on page 1074)

NEWS & VIEWS
ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics, The Canadian Medical Association

NOV. 4, 1961, NUMBER 20

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

Legislation in Saskatchewan

The Saskatchewan Medical Care Insurance Act 1961 appeared in print with remarkable speed after the filing of the Interim Report of the Advisory Planning Committee on Medical Care. So closely did these two productions follow each other that one may be forgiven for wondering whether the draftsmen of the Bill did not actually anticipate the recommendations of the majority of the Advisory Committee to permit the bill to be tabled in the Legislature on October 13, 1961.

The legislation provides the first Canadian example of a health insurance measure which applies to all residents of a province and which can fairly be termed compulsory. Every resident of Saskatchewan, except dependents, must register himself and his dependents in a manner to be prescribed and if he fails to do so or wilfully withholds information he leaves himself open to a fine not exceeding $25.00. Registered persons and their dependents become Beneficiaries under the Act on payment of an unspecified premium, or on having the premium paid on their behalf, and failure to pay such premium is again punishable by a fine not exceeding $25.00.

This, then, establishes beyond question that compulsory, tax-supported medical care insurance is the purpose of the enactment. It is equally clear that the Government and the majority of the Advisory Planning Committee have rejected the repeated recommendations of the medical profession that selective subsidy of the needy and uninsurable elements of the population would be a preferable approach. If one were able to accept that the best method of financing medical care insurance is by compulsory enrolment and taxation, this skilfully-drawn legislation appears to provide a method of implementing the concept.

The official description of the legislation is: "An Act to provide for Payment for Services rendered to Certain Persons by Physicians and Certain other Persons". It will be noted that payment for services rather than the provision of services is its purpose and that the method is termed medical care insurance.

The Interpretation section of the Act consists of a series of definitions including a description of the persons entitled to render insured services. The terminology used in the case of dentists and physical therapists spells out their registered status under The Dental Profession Act 1959 and The Physical Therapists Act, while "'physician' means a duly qualified medical practitioner". The significance of the difference in the words employed is not entirely clear.

Administration by a Commission rather than by the Department of Public Health is provided. The Commission established, however, is not identical with the concept of a "representative, non-political Commission" which we have envisaged. The Commission in this instance "shall consist of not less than six nor more than eight members, of whom one shall be the Deputy Minister of Public Health (non-voting) and at least two others, exclusive of the Chairman, shall be physicians". The Lieutenant Governor in Council appoints all members

and designates the chairman and vice-chairman. It is likely that the chairman of the Commission will be employed full-time but the other members will serve part-time. An unusual provision is that the Commission reports not through its Chairman but through the Deputy Minister of Public Health to the Minister of Public Health and presumably through him to the Legislature. An Advisory Council and a Medical Advisory Committee, both with medical representation, are provided for.

The powers of the Commission are broad and sweeping. They include:

(i) prescribing arrangements for payment to physicians and others providing service.
(ii) prescribing the rates of payments, the method of assessing accounts and the manner and form in which accounts shall be rendered.
(iii) prescribing the terms and conditions on which physicians and others may provide insured services.
(iv) establishing, maintaining and altering lists of persons entitled to receive payments for providing insured services, provided that the appropriate professional body is consulted with respect to the original list and additions and deletions to or from it.
(v) respecting the kind of information to be procured.

The Act does not mention the fee-for-service method of payment for physicians' services but it appears likely that the regulations will spell this out as the usual procedure in personal health services. The legislation does authorize the Commission to make payments to physicians and, subject to a possible utilization charge for certain services, and additional payments to a specialist by a patient who consults him directly, the physician "shall be deemed to have accepted the payment in full for the services".

Premiums are not specified but provision is made for the Lieutenant Governor in Council to levy and collect such premiums as may be authorized. An interesting provision is that where employers have by collective bargaining or otherwise assumed any responsibility for contributing to the cost of health services for their employees they shall continue to do so. It is assumed that premium income will not finance the whole cost and provision is made for treasury appropriations to make up the difference.

Insured services are those services provided or authorized by physicians and specifically the following:

(i) medical services
(ii) surgical services
(iii) maternity services
(iv) new-born care
(v) Specialist services (a) referred
(b) non-referred
(vi) anaesthesia for diagnostic, surgical, obstetrical and dental procedures.
(vii) X-ray, laboratory and other diagnostic procedures, including interpretations.
(viii) preventive medical services (a) inoculation and vaccination
(b) routine physical examinations with certain stated exceptions.
(ix) physiotherapy upon the order of a physician
(x) dental services connected with maxillo-facial surgery
(xi) other services as may be specified by regulation.

It appears to be a noteworthy omission that services in ophthalmology are not mentioned but it is possible that these may be covered under specialists' services. No pharmaceutical benefit appears to be contemplated.

In view of the availability of other programs, and by specific exclusion, the following are <u>not</u> insured services under the Act:

(a) diagnosis and treatment of cancer
(b) medical aid under Workmen's Compensation
(c) services under the following Saskatchewan enactments:
The Tuberculosis Sanitoria & Hospitals Act
The Mental Health Act 1961
The Saskatchewan Hospitalization Act
Part II of the Automobile Accident Insurance Act, or
The Venereal Disease Prevention Act.
(d) medical services provided under the following Federal enactments:
The Aeronautics Act
The Civilian War Pensions and Allowances Act
The Government Employees Compensation Act
The Merchant Seamen Compensation Act
The National Defence Act
The Pension Act
The Royal Canadian Mounted Police Act
The Veterans' Rehabilitation Act
(The status of Indians as beneficiaries is not mentioned)
(e) travelling by a physician
(f) ambulance service
(g) services provided by special duty nurses
(h) any service not rendered by or at the request of a physician
(i) any other services specified in the regulations.

Secrecy is enjoined on all persons employed in connection with the Act in respect of information concerning patients. Freedom of choice of doctor by patients is provided for in respect of insured services and the doctor has the right "to the free acceptance of a patient who is a beneficiary". Procedure for hearing complaints is established and the Act contains the following significant passage:

> "Nothing in this section and nothing done thereunder interferes with the jurisdiction of the College of Physicians and Surgeons of the Province of Saskatchewan under the Medical Profession Act or prejudices the right of any person to appeal to a court of competent jurisdiction".

The Act contains provisions for the collection of premiums, principally through municipal agencies and by means of pay-roll deductions. The joint collection of premiums for hospital and medical care insurance is envisaged. The refund of taxes collected by municipalities for medical care under The Health Services Act is provided for. This suggests that the new provincial plan supersedes the Swift Current program, the community groups now participating in voluntary prepaid medical care plans, and the municipal doctor contracts.

No precise date is set for the inauguration of the new system but it is stated that "This Act shall come into force on the day of assent".

Measuring this enactment by the yardstick of the C.M.A. Statement on Medical Services Insurance several significant deviations are immediately apparent. The most important of these relates to our belief "While there are certain aspects of medical services in which tax-supported programs are necessary, a tax-supported comprehensive program, compulsory for all, is neither necessary nor desirable". The Saskatchewan legislation rejects this view and substitutes a tax-supported comprehensive program, compulsory for all. In this, the legislators are following the pattern established for the provision of hospital care insurance.

Freedom of choice by patient and physician is provided for in both documents. The Act, however, phrases the patients' right to select his medical attendant "from whom he will receive insured services" in a manner which suggests that choice is restricted to those doctors who agree to participate. No provision for the reimbursement of patients who choose to be attended by non-participating doctors within Saskatchewan is provided.

Since the Saskatchewan Medical Care Insurance Commission appears to have no taxing authority and since the premiums and the amount of contribution from other tax sources will be determined by the Lieutenant Governor in Council, the Commission lacks the fiscal authority and autonomy which we have stated to be essential. The consequence of this is that the medical care plan will be competing for its share of the tax dollar with all other responsibilities of Government and it is not difficult to foresee that financial stringency may curtail the ability of the Commission to develop the plan in a progressive manner or even to maintain it adequately.

Much of the detail of important administrative arrangements remains to be decided by regulation. The regulatory powers of the Lieutenant Governor in Council relate mainly to the broad financial aspects of the medical care insurance plan and provision is made for consultation of the Commission. The Commission itself appears to have umlimited powers beyond this point to prescribe the terms and conditions on which physicians and other persons may provide insured services to beneficiaries. It is essential that consultation and negotiation with the appropriate professional bodies be undertaken before regulations are promulgated.

At the time of writing, there appears to be little prospect that the measure will not be passed by the Legislature of Saskatchewan or that it will be substantially modified in the process. It embodies the main issue on which the last election in that province was contested and incorporates the principles enunciated by Premier Douglas, somewhat modified by subsequent studies of the Advisory Planning Committee on Medical Care. However, it lacks the full endorsement of the fifth principle which Premier Douglas enunciated, that the plan "must be in a form that is acceptable both to those providing the service and those receiving it". It represents a development which has been hanging over our heads for many years and one which many doctors have regarded with apprehension. It provides a method for financing medical services which will bear heavily on the tax-payer but which makes no inherent provision for the improvement of health services. Quality of care remains where it always has resided, in the hands of doctors who by training and tradition, strive to apply for the benefit of their patients the best that their art and science can offer.

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The initial reaction of the College of Physicians and Surgeons of Saskatchewan is to refuse to participate in the plan. The resolutions of the Annual Meeting of October 17-20 are not available but it is understood that an overwhelming vote of the meeting declared the legislation to be unacceptable to the profession.

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Reference:

Intravenous Heparin—Its role in the Management of Acute Thromboembolic Diseases.

W. Ford Connell and George A. Mayer
Applied Therapeutics, May 1960, Vol. 2, No. 5, 371-375.

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(Continued from page 1068)

stimulating adventure of the mind, but the brilliant imagination displayed is only slightly hampered by consideration of factual details. For example, dimensional analysis is used to predict that the width of the trunk of animals should depend on the 3/2 power of its length. The logarithmic plot, showing that this may be true, includes "dog". One may well ask, what sort of dog, bulldog or dachshund? Perhaps it is a "mean" dog. The use of logarithmic scales in all the graphs obscures the real lack of agreement between fact and theory. In some places biophysical colleagues might challenge the basic principles and assumptions used. In the chapter on the heart and rate of heartbeat, the effect of size of heart on the mechanical advantage of the heart muscle tension (Laplace's law) appears to be ignored. Underlying the body of the book is the author's "Principle of Optimal Design". Biologists will denounce this as "teleology". Nevertheless it is most valuable to compare the theoretical optima with the facts of biology, but models can be most dangerous unless the purpose is to discover the important omissions and errors in the assumptions of the theory. Rashevsky triumphantly predicts the diameter of capillaries as 2.2 microns, and states that they are observed to be 4.4 microns, yet he started the chapter by stating that "Their diameter is essentially limited by the size of the red blood cells" (whose diameter is certainly more than 7 microns).

Part 3 of the book on the "Principles of Biological Epimorphism" is at a much more advanced level, and stimulating to the basic biological scientist, but demands much more competence in abstract ideas and terminology than the average M.D. would possess. This book is recommended for enjoyment and stimulus, but should be taken with many a pinch of salt. Its value to the reader depends on his being aroused to challenge rather than to accept uncritically Dr. Rashevsky's steps of logic. Physiologists, biochemists, biophysicists and physicists seem much more likely readers than those whose chief occupation is the practice of medicine.

ATLAS OF HUMAN ANATOMY. 3 Volumes. Ferenc Kiss and Janos Szentagothai. Publishing House of the Hungarian Academy of Sciences, Budapest, 1960.

The first Hungarian edition of this atlas of human anatomy was published between 1946 and 1951. This was followed by two revisions in Hungarian and by two German, one Russian and Bulgarian and one Chinese edition. The atlas appears to be well established and widely used in countries in the sphere of influence that includes Hungary. The 1960 edition of the atlas is the first in English. The authors are known internationally as productive investigators of a variety of anatomical subjects.

A conventional organization for atlases of gross anatomy is followed. Volume 1 deals with the skeleton, joints and muscles, Volume 2 with the viscera and Volume 3 with the nervous and vascular systems. The majority of the illustrations are in colour. There are included several three-dimensional drawings of the type that is more likely to be found in textbooks of histology, e.g., diagrams of the intestinal mucosa, hepatic and pulmonary lobules, cochlear duct, etc. Several drawings of cross-sections through the brain stem are included. The Basle anatomical nomenclature is followed. The quality of paper and binding is excellent.

A great deal of meticulous work has obviously been put into this three-volume atlas. The material included is similar to that found in atlases of gross anatomy that are now used in Canadian medical schools. In general, the quality of the illustrations is not superior to that of atlases now used by our medical students. Thus, one would not expect the books by Kiss and Szentágothai to replace similar works now being used in this country. But the atlases from Hungary will no doubt continue to be valuable in medical education in countries where similar works are perhaps less favoured or less readily available.

SYMPTOM DIAGNOSIS. 5th ed. Wallace Mason Yater and William Francis Oliver. 1035 pp. Appleton-Century-Crofts, Inc., New York, 1961. $15.00.

The word "symptom" in the title means both subjective and objective manifestations of disease, for it includes physical signs. The authors have provided a well-organized, exceedingly comprehensive guide to diagnostic possibilities. The book is designed for rapid reference: concise in style and abbreviated by cross-references. So much detail would overwhelm most undergraduate students but could help the doctor by suggesting possible diagnoses in difficult cases. Medical gamesmen will welcome the lengthy lists of eponyms at the back.

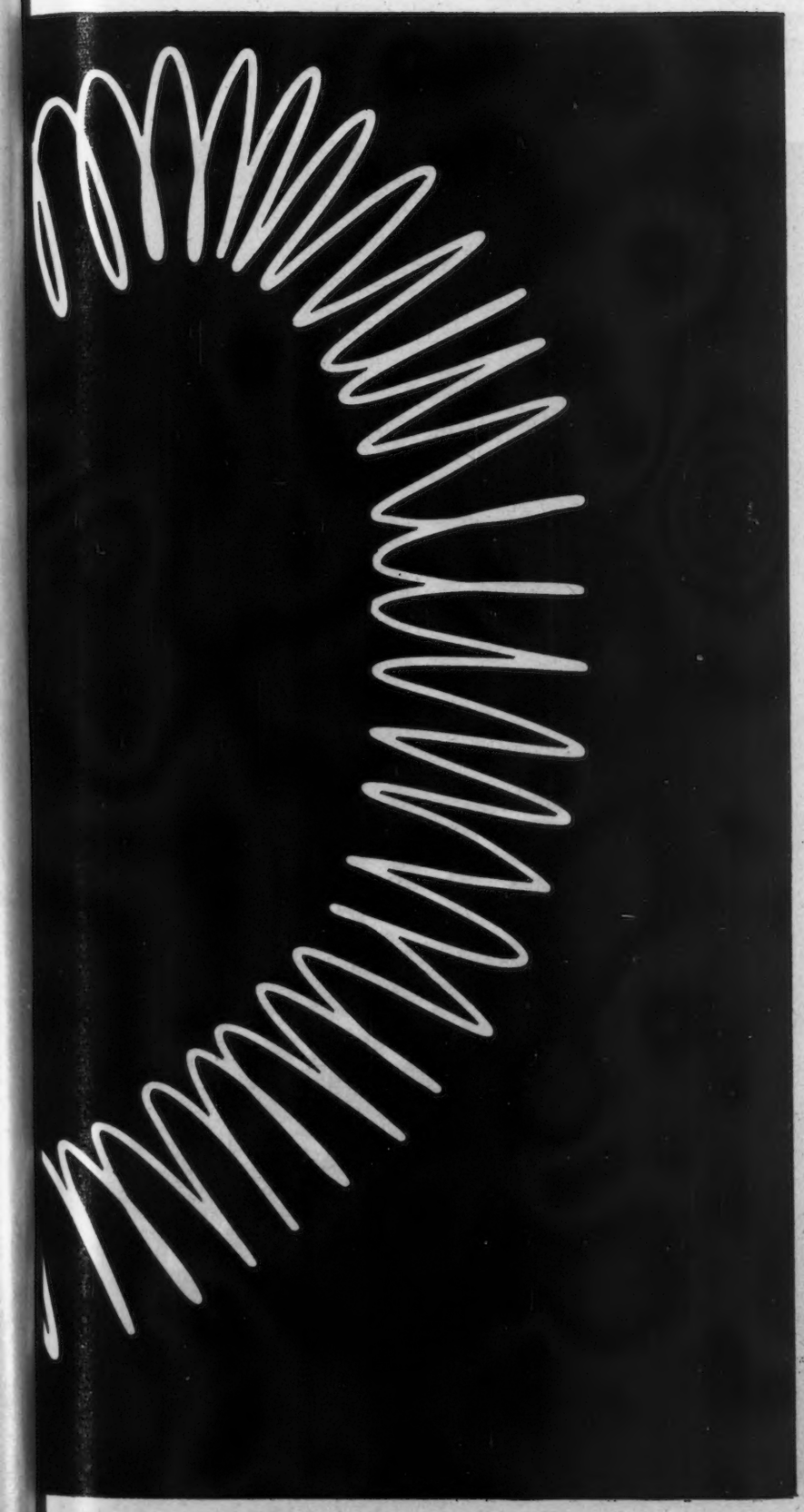
PHARMACOLOGY AND ORAL THERAPEUTICS. 12th ed. Edward C. Dobbs. 578 pp. Illust. The C. V. Mosby Company, St. Louis, Mo., 1961. $10.00.

It is quite apparent that the author of this book is very conversant with the teaching of pharmacology to the students of dentistry and also with the problems of the practitioners in this field. The book touches succinctly on all subjects in pharmacology and tends to dwell on the fundamental tenets of the different areas. It is remarkably concise and yet almost sufficient in providing pertinent information on the subject as a whole. The general format of the book is pleasing to the eye. The arrangement of each chapter has been very cleverly executed with the help of different letter types. The language has a quality of simplicity that makes for easy reading. Historical notes add zest to the chapters.

In this edition the book has been brought quite up-to-date. The chapters have been rearranged so there is an excellent dovetailing of the materials in logical order. New categories have been included and new chapters added. Pharmacopeia of the United States (1960), National Formulary (1960), New and Nonofficial Drugs (1961), and Accepted Dental Remedies (1961) have been consulted. Recent ideas in the treatment of various maladies have been incorporated.

The book, however, is not entirely devoid of flaws. Chapter nine, for example, is entitled "Drugs Which Affect the Genitourinary System," but deals only with the urinary system. Occasionally a diagram appears lacking proper reference to the source. The bibliographies are often too few and insufficient. Apart from these few inadequacies, the book on the whole appears to be accurate.

It is recommended not only to students and practitioners in dentistry, but also to those who would like to revise and refresh their knowledge of pharmacology in a limited time.



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1. H. A. Bowes, Dis. Nerv. Syst. *21:* (Suppl.) 20-22, 1960.
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MEDICAL NEWS *in brief*

(Continued from page 1060)

THE NEED FOR REGULATION OF AMBULANCE SERVICES

In recent years a few communities in Canada have been turning their attention to the problem of operation of road ambulance services. Saskatchewan first had provincial regulations governing road ambulance services in 1946 but they were minimal and unfortunately rarely enforced. In 1957 it became evident that a survey of provincial ambulance services was needed in order to determine what standards should be enforced in Saskatchewan. The results of this survey are reported by Williams (*Occup. Health Rev.*, 13: 15, 1961).

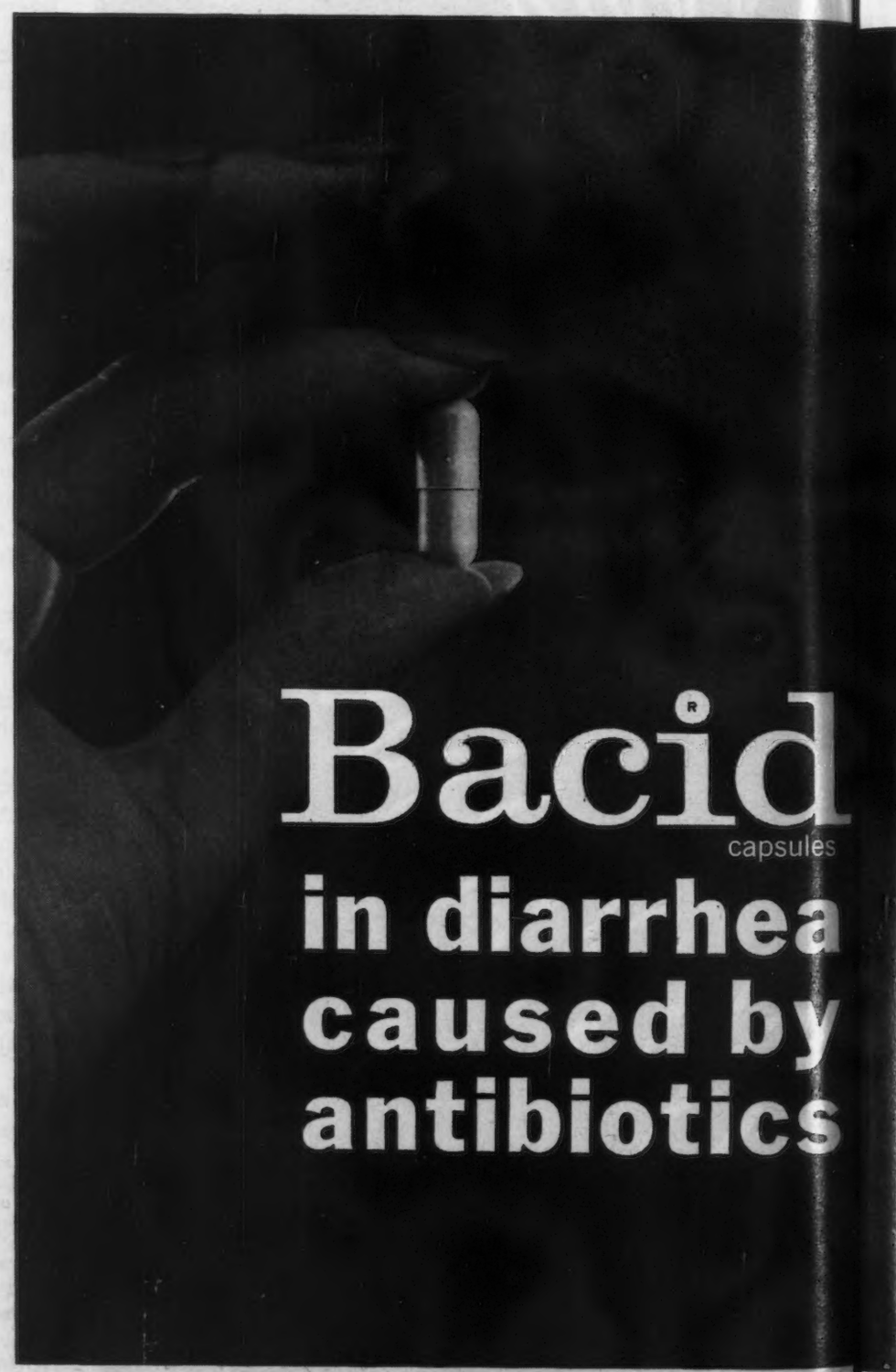
The majority of ambulance services in Saskatchewan are operated by funeral homes. In pioneer times it was probably only the undertaker who had a vehicle which would transport a lying case in reasonable comfort. Embalming processes required some knowledge of anatomy by the undertaker's staff, so it was logical that they should be the persons to give first-aid when required. The fact that their work could, without serious detriment, be postponed for an hour or so was an additional reason why undertakers operated early ambulance services.

In the larger cities the trend has been towards the development of what might be called professional ambulance services doing nothing but ambulance work. This divorce from the undertaking business has created financial problems of operation by city services and has led to the granting of subsidies by the councils of some cities.

Hospitals in two of the smaller cities operate their own ambulance services. In one, a local taxi service provides the driver as required, and in the other the hospital radiographic technicians make up the crew. There are also two municipalities who operate ambulance services, these in each case having been taken over from a privately operated service to maintain a service which otherwise would have been abandoned; and finally there are a few individuals in small communities with none of the connections listed above who operate an ambulance service, usually taking no more than a dozen calls in a year.

Diverse as these ambulance services are in their operation, they all have one thing in common — they have real and severe financial difficulties. The reason is easy to understand when one considers the cost of vehicles and equipment, the necessity of being on 24-hour call, and the inevitable low percentage of utilization. This has resulted in difficulty in paying wages sufficient to attract and retain good and experienced attendants, this being especially a problem of the professional ambulance services.

All services are required to register annually with the Minister of Public Health. This enables the Department to arrange for inspection of the services in regard to sections of the regulations dealing with training and equipment. The registration information concerning the numbers of trained person-



nel and vehicles is surely a statistic any public health department should have for its province. It also provides a mailing list for forwarding technical information concerning supplies and equipment and the details of the advanced first-aid courses held annually.

Training

The first requirement is that every ambulance must have one attendant who holds a valid St. John Ambulance Association First Aid Certificate. In the author's opinion this does not go far enough. It is possible to obtain this certificate without receiving any teaching from a member of the medical profession. Even during the examination for the certificate the candidate may meet the physician only briefly. The medical profession should and must take more responsibility for the training of these professional first-aiders. There are many specialized first-aid problems and techniques which the ambulance crews have to cope with but which are not dealt with in the standard first-aid text books. Examples include the care of certain emergency medical cases in transit, emergency obstetrics, the use of oxygen, aspirators and resuscitators, and the extrication of persons with multiple injuries from crashed cars. The medical profession has with good reason been critical of some of the first-aid care given, but it cannot continue criticizing unless it shoulders some of the responsibility for ensuring a high standard of first-aid care.

The consensus among the ambulance operators is that the courses are of considerable value to them. For the first time they feel that they are recognized as a service group by the medical profession and the government. The courses also enable ambulance service operators and attendants to meet each other and discuss topics of common interest. One result has been the formation of the Saskatchewan Road Ambulance Association which is beginning to take an active interest in the planning of ambulance services in the province.

Ambulance services have not received the attention they have deserved from government, the public and the medical profession. If victims of accidents and illness are not to receive second-class rides, measures have to be taken to improve standards of ambulance services. This implies basic regulations, a training program and in many instances some form of financial support.

ENTERIC VIRUSES IN WADING POOLS

The isolation of viruses from urban wading pools by Kelly and Sanderson (*Pub. Health Rep.*, 76: 199, 1961) indicates that a potential health hazard may exist. It may be significant that no virus was isolated from samples of the pool having the lowest coliform density. The failure to detect viruses in chlorinated swimming pools sampled during the same period and in the same area suggests that similar treatment of wading pools is needed.

(Continued on page 44)

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Canad. M. A. J.
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MONTREAL CANADA

MEDICAL NEWS *in brief*

(Continued from page 35)

ERADICATION OF POLIOMYELITIS

The extensive field trials of 1959 on millions of susceptible persons of various ages not only established the safety and effectiveness of the oral, live poliovirus vaccine but also suggested the possibility that the disease, as well as the causative paralytic viruses, could under certain conditions be completely eliminated. This is theoretically possible with the oral live vaccine, which gives rise to varying degrees of resistance to reinfection of the intestinal tract, but not with the killed virus vaccine, which, while protecting the individual against paralysis, does not prevent him from becoming a carrier.

A program for the eradication of poliomyelitis has been outlined by Sabin (*Ann. Int. Med.*, 54: 1057, 1961). The first steps in the attempt to eradicate poliomyelitis were taken in 1960 in many countries outside the U.S.A., where more than 85 million persons received the oral vaccine, and in the cities of Cincinnati, Ohio, and Rochester, N.Y., in the U.S.A., where about 300,000 persons received this vaccine in community-wide programs. The results obtained in 1960 indicate that community-wide programs of sequential feeding of all three types of the vaccine during a period of several months can rapidly eliminate poliomyelitis. In Cincinnati, where about 75% of the children from three months to 18 years of age received the oral vaccine, there was not a single case of poliomyelitis in either the vaccinated or the unvaccinated in 1960, and 100% of the non-immunes who received the vaccine developed immunity. Furthermore, virologic studies indicated that the polioviruses practically disappeared from the community in about three months after administration of the last dose of the oral vaccine.

A program for the eradication of poliomyelitis in the U.S.A. by means of the oral vaccine would involve two phases: (1) community-wide immunization of the largest possible number of susceptibles in a single year during the winter and spring months, followed by (2) immunization of all newborn children during the first year of life as part of their regular medical care.

DESTRUCTIVE LESIONS OF THE VERTEBRAL BODIES IN RHEUMATOID DISEASE

Seaman and Wells have reviewed the roentgenograms of 110 patients with Marie-Strümpell ankylosing spondylitis (*Am. J. Roentgenol.*, 86: 241, 1961). This review disclosed 11 patients with destructive lesions of the vertebral bodies. In addition, two patients were found to have peripheral rheumatoid arthritis. Several others had definite but minimal sclerosis and erosion, but these were not included in the study.

The 11 cases of Marie-Strümpell arthritis with destructive lesions of the spine have certain features in common. The destruction begins anteriorly and remains relatively stationary but may progress to involve the entire articular surfaces of the vertebrae. The disc space is not always narrow. All of the patients had involvement of the sacroiliac joints, and all had had symptoms for one year or more. Four of the 11 patients were females. Most of the patients complained of moderate to severe pain in the region of the destructive process.

The roentgenographic findings are of two main types. They both begin as a tiny focus of destruction near the upper or lower anterior corner of a vertebral body associated with varving degrees of sclerosis of the adjacent bone. In one, this focus of destruction progresses to involve the entire extent of the cortical end plates of the adiacent vertebral bodies. In the other it remains localized to the anterior corner of the vertebral body.

The roentgenographic appearances may be indistinguishable from those produced by tuberculous, staphylococcal, typhoid, paratyphoid or Brucella infection of the vertebrae. There are a few minor differences in that, with bacterial infections, narrowing of the intervertebral disc usually precedes the roentgenographic evidence of bone destruction, while in ankylosing spondylitis and rheumatoid arthritis bone erosion is frequently demonstrable without disc narrowing and occasionally even with disc widening. Paravertebral masses are frequently associated with bacterial osteomyelitis but are rare in the rheumatoid diseases.

The role of steroid therapy in the pathogenesis was difficult to

(Continued on page 48)

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Codeine phosphate in a slow-release core	½ gr.	Gives PROLONGED Relief

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Canad. M. A. J.
Nov. 4, 1961, vol. 85

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A 1940 newspaper stopped him cold!

He found it rummaging through an old trunk. The story of the Dunkirk evacuation was there, recalling his own decision to enlist.

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Age by age, life insurance costs are almost the same—often lower—than in 1940. Also, the people who started protection then, pay no more today than they did 20 years ago. Even when other prices are inflated, life insurance is the only investment which protects your dollars as it protects your family.

Here are some of the reasons

- Permanent life insurance values are stable and can show healthy growth through the payment of annual dividends.
- Other investments, such as real estate, common stocks, *even bonds*, carry an element of risk, and records show they can decline even while living costs rise.
- Since insurance premiums are spread over many years, you pay with dollars that are averaged out over both low and high cost periods.
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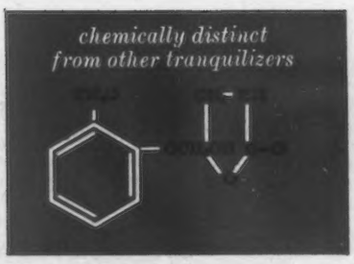

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MEDICAL NEWS *in brief*

(Continued from page 45)

assess. It is certainly not the sole cause, as five patients in this series were not treated by steroids.

In addition to the main theme of the paper as indicated in the title, there is a section on atlanto-axial subluxation. This complication occurred in a patient with peripheral rheumatoid arthritis who also had a destructive process involving the interspace between the 5th and 6th cervical vertebrae. Laminagraphic studies also revealed bone erosion of the surface of the odontoid and the anterior arch of the atlas. There was no evidence of cord compression. A second patient not included in the series, with peripheral rheumatoid arthritis, had a less severe atlanto-axial subluxation but no neurologic findings. A third patient with ankylosing spondylitis, also not included in the series, showed atlanto-axial subluxation but no bone destruction.

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OVERSEAS SUBSCRIPTION RATES, BRITISH MEDICAL JOURNAL

Effective January 1, 1962, the overseas rate for subscriptions to the *British Medical Journal* will be increased from £2.12.6 per annum to £3.3.0 per annum.

PHENACETIN-INDUCED CHRONIC INTERSTITIAL NEPHRITIS

The first detectable evidence of chronic interstitial nephritis is a reduction in renal function, but symptoms are few at this stage and, as a result, the patient frequently presents only later when uremia and anemia develop. Urinary findings are characteristically few throughout the course of the disease. The serum proteins are usually normal; nephrotic edema is rare; and elevation of the blood pressure occurs late.

Histologically, chronic interstitial nephritis is characterized by a marked increase in the amount of the interstitial fibrous tissue of the kidney, with atrophy and destruction of the renal convoluted tubules. The glomeruli and vessels remain mostly intact, but occasional glomeruli may be hyalinized, and the arterioles may show some hyalinization. The interstitial tissue is infiltrated with lymphocytes and plasma cells together with a few acute inflammatory cells. Macroscopic and microscopic areas of papillary necrosis are found frequently and are characteristic.

The precise pathogenesis of chronic interstitial nephritis from excessive phenacetin ingestion is not clearly established.

It has been established that the incidence of reduced renal function increases with the intensity of dosage, and the duration of administration of phenacetin. Although the amount of phenacetin necessary to cause renal damage is variable, 1 gram or more daily for a prolonged period is certainly dangerous.

These characteristic clinical and pathological features of chronic interstitial nephritis due to excessive phenacetin consumption are discussed, and an illustrative case history is presented by G. Buchanan in the *New Zealand Medical Journal* (60: 207, 1961). A more recent article, by Lakey, has appeared in this Journal (*Canad. M. A. J.*, 85: 477, 1961).

POSTGRADUATE COURSE IN ALLERGY

A continuous course of two weeks' duration is being offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center from 9.00 a.m. to 5.00 p.m. from March 5 to March 16, 1962. The tuition fee is $175.00, and enrolment is limited. Dr. Louis Tuft is course director and Drs. George I. Blumstein and Merle M. Miller are associate directors.

An outstanding faculty has been assembled to review the basic principles of immunology and allergy as applied to clinical practice. Emphasis will be given to the methods of diagnosis and management of the allergic patient. The pediatric and dermatologic aspects of allergy will be presented at clinical seminars especially arranged to demonstrate the problems encountered in these fields.

The course is designed for physicians desirous of extending their knowledge of allergy. It could serve as an introductory course for those about to enter the field or as a review course for practising allergists.

For brochure and application forms write to: Dr. George Blumstein, c/o Temple Medical Center, Philadelphia 40, Penna., U.S.A.

A NEW TECHNIQUE IN THE DIAGNOSIS OF HIRSCHSPRUNG'S DISEASE

The diagnosis in most cases of congenital megacolon has in the past rested on demonstrating an absence of myenteric nerve plexuses on microscopic study of a full-thickness segment of lower bowel, i.e. demonstrating an absence of ganglion cells from Auerbach's (intermuscular) plexus. More recently, Bodian has suggested that a mucosal biopsy is also a reliable method if it can be shown that ganglion cells are not present in Meissner's submucosal plexus.

Shandling (*Canad. J. Surg.*, 4: 298, 1961) has investigated another method, namely biopsy of a valve of Houston, to demonstrate this diagnostic feature. In eight children or newborn infants with Hirschsprung's disease, he noted ganglion cells to be absent, whereas in 32 other patients without this disease, but with unrelated conditions, these cells were always found.

The theory underlying this method is based on the observations of Gabriel, that the curves of the rectum are accentuated on their concave aspects by infoldings of the whole thickness of the rectal wall which constitute the valves of Houston. Normally these sites should contain ganglion cells of both myenteric plexuses, and their absence should be of diagnostic significance.

Obtaining such a biopsy is facilitated by distension of the rectal ampulla with air. A modification of a Lloyd Davis child's sigmoidoscope to permit this was found useful.

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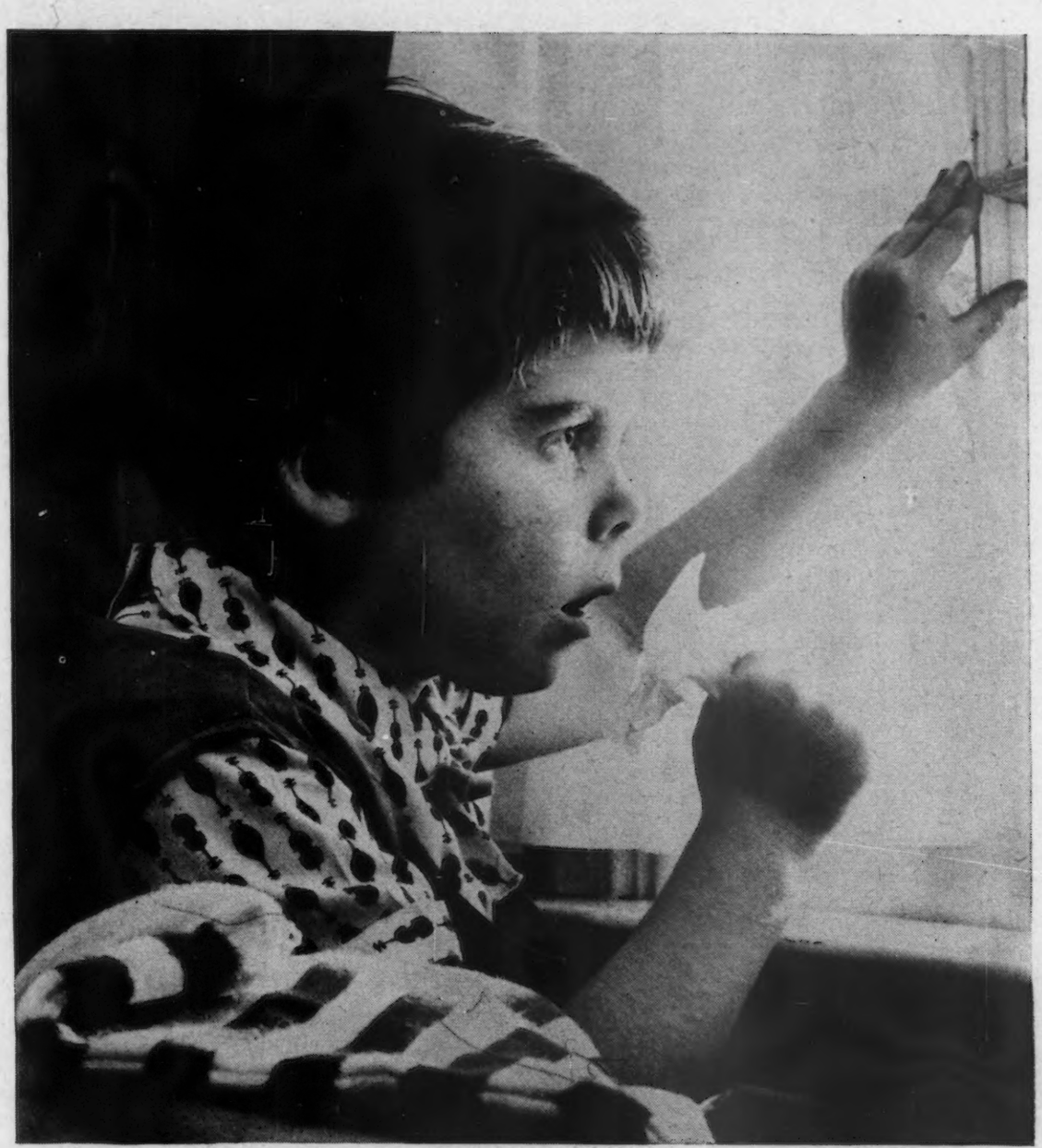

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PROVINCIAL NEWS

BRITISH COLUMBIA

Dr. Carl J. Reich, Chairman of the Westminster Medical Association's Committee for Salvage of Used Medical Journals, has informed the *Journal* that the first shipment of used medical periodicals collected in B.C. by the joint efforts of physicians, druggists and pharmaceutical detail men was despatched on September 5 and was due to arrive in Karachi, Pakistan, on November 1. This shipment consists of approximately 95 complete volumes of the *Canadian Medical Association Journal* of 1956 to 1960 vintage. These volumes will be distributed among medical libraries in West Pakistan by the Pakistan Medical Association and its Journal.

It is anticipated that pharmacists and pharmaceutical detail men will continue to extend their assistance and co-operation in centralizing such donations in Vancouver where sorting and crating of the January to June 1961 issues will take place in November, and of June to December 1961 issues, in April or May of next year. Dr. Reich reiterates his request to members of the medical profession in British Columbia to support this program of salvage by saving all back copies of their journals for this purpose.

ONTARIO

Dr. P. Wildy of the Department of Virology, University of Glasgow, recently presented an address at the Ontario Cancer Institute on "The Structure of Viruses". Until recently, Dr. Wildy was a member of the group at Cambridge, England, who by developing the negative staining method in electron microscopy, contributed a material advance in the knowledge of the structure of viruses and macromolecules.

The annual report of the College of Physicians and Surgeons of Ontario draws attention to the fact that one of its most difficult problems is the supply of new doctors. Since the Second World War, 6130 new licences have been issued for the practice of medicine in this province. Ontario has one physician to 706 people. The medical population has increased at a more rapid rate than the population as a whole. But the peak of post-war registration was reached in 1956 when 522 licences were granted. Each year since has shown a decline. In 1960, 401 licences were granted. At present there are 1100 interns in Ontario hospitals; of these, 385 are graduates of foreign medical schools.

The tuberculosis death rate in Ontario in 1960 was the lowest in Canada. The mortality rate was 2.6 per 100,000 population and the number of deaths totalled 157 (110 males and 47 females). Tuberculosis is now a disease of older people, with its highest death rate among those over 60 years of age. In the group between 60 and 69 years there were 36 male deaths and 7 female, while the figures for those over 70 years showed 36 male deaths and 18 female.

The province with the next lowest rate is Alberta, where the rate was 2.7 per 100,000. The death rate for Canada as a whole is 4.6.

The Toronto Academy of Medicine and the Workers' Educational Association are jointly sponsoring a series of 10 lectures to be given by Fellows at the Academy. The first lecture was on alcoholic addiction. Subjects for later talks include cancer, diseases of the eye, diseases of the nervous system, diseases of the heart, mental disorders, arthritis, orthopedic surgery and public health.

Dr. Keith Welsh, Surgeon-in-Chief at St. Michael's Hospital, Toronto, has been appointed exchange professor for six weeks at Middlesex Hospital Medical School, London, England. LILLIAN A. CHASE

PRINCE EDWARD ISLAND

The Hospital Association of Prince Edward Island held its first Institute for Hospital Trustees on September 21. The Institute, under the general chairmanship of Judge J. S. DesRoche, president of the Association, was attended by more than 60 people. Nearly half of the registrants were hospital trustees representing all the hospitals of the Island. In addition, there were representatives from the medical staffs and administrative personnel. The Hon. Hubert B. McNeill, M.D., Minister of Health, welcomed the delegates at a dinner in the Charlottetown Hotel.

The program was presented in four parts which dealt with the changing aspects of trustees' responsibility. Guest speakers were: Dr. W. I. Taylor, Executive Director of the Canadian Council of Hospital Accreditation; Dr. W. Douglas Piercey, Executive Director of the Canadian Hospital Association; and Lawrence L. Wilson, Assistant Director (Education), Canadian Hospital Association, Toronto. Dr. Piercey spoke on "The Trustee in Organization and Management" and "The Medical Staff and Medical Care". Mr. Wilson discussed "Trustee Relationships" and Dr. Taylor spoke on "The Hospital Accreditation Program as a Measuring Device". In the course of his remarks Dr. Taylor pointed out that more hospitals are now meeting the standards of the Accreditation Council and that, in general, hospitals in the Maritimes had made excellent progress in the accreditation program.

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1. Miller, J., and Fishman, A.: A Serotonin Antagonist in the Treatment of Allergic and Allied Disorders (to be published).
2. Kaminsky, H. and Astrilant, M.: The Therapeutic Action of a New Antiserotonin Agent in Dermatology, Dia Médico 34:1970-1973, Sept. 8, 1960.

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ABSTRACTS

MEDICINE

Purified Poliomyelitis Vaccine—Clinical Appraisal.

C. WEIHL, D. CORNFELD, H. D. RILEY, N. HUANG AND H. CRAMBLETT: *J. A. M. A.*, 176: 409, 1961.

A new-killed purified poliomyelitis virus vaccine is described in which the amount of antigen for each poliovirus type was precisely standardized, by physical and chemical methods, to provide a vaccine of uniformly high potency. The purification process was successful in removing all serologically detectable monkey-kidney antigen (thus obviating the theoretical problem of renal autoimmunization), and essentially all the other non-viral contaminating material present in the ordinary crude Salk vaccine.

It was found that two doses of 0.5 ml. each, given one month apart, elicited significant responses of neutralizing-antibody to Parker Type-I poliovirus in 98% (52 out of 53) of initially sero-negative children. Comparable responses were obtained with respect to the Type-II MEF-1 and Type-III Saukett types of polioviruses.

The authors believe that this purified vaccine fills the important public health need for a poliomyelitis vaccine that will consistently, rapidly and safely immunize essentially all recipients against all three poliovirus types.

FRANCES LETTAU

Recent Trends in Therapy of Cerebral Vascular Disease.

S. N. GROCH AND I. S. WRIGHT: *Circulation*, 23: 458, 1961.

In a discussion of the various measures available for the therapy of a patient with a stroke, the value of vigorous conservative therapy is emphasized. The role of anticoagulant drugs is outlined: this mode of treatment seems most efficacious in recurrent transient ischemic attacks and the slowly progressive stroke. The value of anticoagulants in the acute phase of cerebral thrombosis and in long-term postinfarction therapy is not as yet clear. The role of anticoagulant drugs in treatment of cerebral embolism seems well established. It may be wise to delay institution of these drugs for 24 to 36 hours after the acute stroke. Surgical procedures give promise of value in certain well-defined syndromes. The patient with cerebral hemorrhage still remains a formidable therapeutic problem.

S. J. SHANE

Growth and Development of Children with Galactosemia.

G. N. DONNELL, M. COLLADO AND R. KOCH: *J. Pediat.*, 58: 836, 1961.

Observations on the growth and development of 15 living galactosemic children from 16 families, and data on the effects of dietary management in relation to the attainment and maintenance of optimal intellectual capacity are presented.

The physical growth patterns of all but three of the children studied were within normal limits. The intellectual abilities of the parents of the children were normal, and all but one of the siblings were also normal. By contrast, four of the galactosemic children were mentally defective, and one of them was in a state hospital for retarded children: six other children had borderline intelligence; and a further six were in the low-normal to normal range. Only three of the galactosemic children had an intelligence quotient of over 100.

When dietary management was started late, there was a greater incidence and severity of mental handicaps. Strict adherence to a galactose-free diet is suggested, and it is recommended that soya products be avoided until additional knowledge is available regarding their significance in this disorder.

FRANCES LETTAU

Studies on Digitalis. III. Influence of Triiodothyronine on Digitalis Requirements.

R. L. FRYE AND E. BRAUNWALD: *Circulation*, 23: 376, 1961.

The effect of triiodothyronine administration on digitalis requirements was studied in a group of patients with atrial fibrillation. The ventricular rate was utilized to provide a quantitative expression of digitalis effect. In one patient the amount of acetylstrophanthidin, administered as a constant infusion, required to slow the ventricular rate to 70 beats per minute, rose from an average of 0.58 mg., while the patient was myxedematous, to 1.50 mg., when he was euthyroid. When mild thyrotoxicosis was induced in three euthyroid patients, the daily dose of digoxin had to be increased approximately four-fold in order to maintain the ventricular rate at a control level. In three patients it was observed that reserpine or syrosingopine administered intramuscularly abolished the increased requirements for digoxin induced by triiodothyronine. In two patients syrosingopine was found to prevent partially the tachycardia resulting from large doses of intravenous triiodothyronine. The possible mechanisms responsible for these effects and their therapeutic implications are discussed.

Chronic Spontaneous Cerebrospinal Rhinorrhea.

W. M. ANDERSON, G. A. SCHWARZ AND G. D. GAMMON: *Arch. Int. Med.*, 107: 723, 1961.

Three cases in which chronic cerebrospinal rhinorrhea occurred spontaneously but secondary to intracranial neoplasms are reported. A review of the literature is presented, which shows that the occurrence of such events is a rarity.

In each of the three patients in this series, a sellar neoplasm was demonstrated. One of the most dangerous complications of cerebrospinal fluid rhinorrhea, whether spontaneous or secondary to one of the other causes, is infection of the leptomeninges. In this series regular and continuous use of antibiotics proved to be a persistently effectual and harmless prophylaxis against leptomeningitis. Roentgen irradiation of the sellar neoplasm seemed beneficial in controlling the growths.

The methods of identification of the nasal fluid are outlined. Cerebrospinal fluid rhinorrhea was suggested by the profuseness of the discharge, the lack of associated allergic rhinal disease, and the character of the fluid. Verification of its nature included determinations of specific gravity and of chemical constituents,

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References: **1.** Spielman, A.D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. **2.** Alfaro, R. D., Gracanin, V. and Schlueter, E.: J. Lancet (in press). **3.** Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959.

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more specifically, quantitative estimation of protein and sugar.

The need for a corrective surgical procedure for cases of this type is suggested; possibly, by combining the skills of the otolaryngologist and the neurosurgeon, a corrective surgical procedure may be developed.

FRANCES LETTAU

Chronic Respiratory Disease in a Random Sample of Men and Women in the Rhondda Fach in 1958.

I. T. T. HIGGINS AND A. L. COCHRANE: *Brit. J. Indust. Med.*, 18: 93, 1961.

The high death rates for bronchitis in South Wales miners were investigated by means of a survey of respiratory symptoms and ventilatory capacity on 90% of a random sample of 600 men between the ages of 35 and 64, and 200 women between 55 and 64 living in the Rhondda Fach. The sample of men was stratified by age and occupation: 100 miners and ex-miners, and 100 non-miners were studied in each decade.

A higher prevalence of symptoms and lower maximum indirect breathing capacity (I.H.B.C.) was found in miners and ex-miners, and within the mining group there was little relation of symptoms to radiological category of pneumoconiosis. Miners and ex-miners with progressive massive fibrosis were found to have a lower mean I.M.B.C. than the rest at all ages.

Analysis of symptoms and I.M.B.C., by length of time spent working on the coal-getting shift, in both miners and ex-miners did not indicate that the total dust dosage to which the man had been exposed during his working life was closely related to chronic respiratory disease. It was found that those who had worked for less than one year on the coal-getting shift had a lower prevalence of symptoms and a higher I.M.B.C. Above one year there was no clear pattern of symptom prevalence although there was a slight downward trend in the mean I.M.B.C. with increased time spent working on the coal-getting shift. When working miners alone were considered, the reduction in ventilatory function with increasing duration of work was slightly increased.

Dust exposure alone appeared unlikely to account for all the excess respiratory disease in miners compared with the rest of the community; other explanations are discussed.

The women studied had a lower prevalence of symptoms than the men who had never worked in mining. However, this prevalence was higher than that found previously in rural areas of Wales and Scotland. The mean I.M.B.C. of women in this survey was also lower than that found in Scots women. Analysis of the findings showed that miners' wives had a higher prevalence of symptoms and a lower mean I.M.B.C. than non-miners' wives, suggesting the importance of social factors rather than occupational factors in miners.

Smoking was found to be associated with an increased prevalence of symptoms and a lower mean I.M.B.C. in men, but not in women. However, differences in smoking habits could not account for the differences between miners and non-miners, as these remained after standardization for smoking.

FRANCES LETTAU

SURGERY

Simplified Treatment of Large, Sacciform Aortic Aneurysms with Patch Grafts.

E. S. CRAWFORD, M. E. DEBAKEY AND F. W. BLAISDELL: *J. Thorac. Cardiovasc. Surg.*, 41: 479, 1961.

Simple excision of sacciform aneurysms distal to the occluding clamp and closure of the aortic opening by suture, as employed in lesions involving a small part of the aortic circumference and attached by a narrow neck, is not applicable to aneurysms with relatively large necks whose sacs roll over to incorporate much of the aortic wall. It is difficult, if not impossible, to apply an occluding clamp across the base of such aneurysms without causing severe constriction or complete occlusion of the aortic lumen. Moreover, repair of these aneurysms may cause severe encroachment on the normal aortic lumen. Therefore, complete excision of the involved aortic segment with graft replacement may be necessary, a procedure of considerable magnitude.

It has proved possible to eradicate such lesions by a much simpler procedure, consisting of excision of the aneurysmal sac and closure of the aortic opening with a patch graft. This has the advantage of being relatively simple, as evidenced by the great reduction in the amount of blood lost and in the duration of the operation in the five cases reported in this paper. (After authors' summary.)

S. J. SHANE

Rhytidoplasty (Face-Lift) for Wrinkles and Redundant Skin About Cheeks and Neck.

J. B. ERICH: *Proc. Staff Meet. Mayo Clin.*, 36: 68, 1961.

A detailed description of the author's technique of rhytidoplasty (face-lift) for wrinkles and redundant skin about the cheeks and neck is presented. "Before" and "after" photographs of four cases in which this technique was used are included for illustration of the results obtained. In general, the results of rhytidoplasty can be expected to remain in evidence for three to five years.

It is the author's belief that there is a definite need these days for the so-called face-lift operation; the reasons for this belief are outlined. A brief discussion of the causative factors of and the degenerative changes which result in wrinkles and redundant skin about the cheeks and neck is presented.

FRANCES LETTAU

THERAPEUTICS

Treatment of Essential Hypertension with Androgenic Hormones.

F. K. FEIKS: *Wien. med. Wchnschr.*, 111: 283, 1961 (German).

This statistical study involved 570 patients, 211 men and 359 women, who were treated for hypertension over a period of four years. Treatment was always begun with bed rest and salt restriction until the blood pressure was stabilized, usually at a lower level than on admission. Medication was then commenced, and depending on the nature of the case, theophylline preparations, nicotinic acid derivatives or ganglion blocking agents were used. Best long-term results were achieved with a combination of hydrochlorothiazide and rauwolfia preparations. About 70% of the patients showed a good or satisfactory response to this

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treatment. In the remaining 30% it was not possible to lower the blood pressure sufficiently. It was decided to treat this group with testosterone in addition to the therapy outlined above. Patients with chronic liver disease, precancerous conditions or a family history of cancer were excluded from hormone treatment. Although there is no proof that male sex hormones are carcinogenic, there is a possibility, according to reports in the literature, that any steroid compounds may be metabolized to form carcinogenic substances. Patients with myocardial infarctions or encephalomalacia were also excluded from hormone therapy. Thus 123 patients were left who received 250 mg. of long-acting testosterone intramuscularly. Sixty-one per cent of these showed a good or satisfactory response, as the blood pressure was lowered by more than 40 mm. Hg or by 20-40 mm. Hg, respectively. The effect of the hormone injections lasted up to four months and could be prolonged by repeated injections as indicated.

The authors analyze their results with regard to age group, degree of hypertension and sex, but the question of side effects, especially in the female patients, is not discussed. KATHERINE E. RICHTER

Tolbutamide in Cirrhosis of the Liver.

I. SINGH, K. B. SEHRA AND S. P. BHARGAVA: *Lancet*, 1: 1144, 1961.

Fifty-five patients (49 males and 6 females) with cirrhosis of the liver were treated with tolbutamide, 1.0 to 1.5 g. daily. Each patient acted as his own control and was given tolbutamide and placebo as described. The effects of the basic, placebo, and tolbutamide treatments on appetite, ascites, weight, serum proteins, serum bilirubin, serum alkaline phosphatase, flocculation tests, and the blood picture, studied at appropriate stages in all cases, are reported.

The outstanding effects of tolbutamide therapy were increased appetite, improvement in general condition, weight gain and control of ascites. Forty-two of the 55 patients showed a progressive decrease in ascitic fluid to nil in from three to 14 weeks. This diminution in ascites was significantly associated with a rise in serum proteins, mainly due to albumin increase, with a variable degree of globulin fall in individual cases. The increase in serum proteins appeared to be due to some specific effect of tolbutamide on the liver. The drug was well tolerated by all patients, and there were no hypoglycemic reactions or other adverse effects.

In the opinion of the authors, tolbutamide has a definite place in the therapy of cirrhosis of the liver.

FRANCES LETTAU

First Experiences with Alupent in the Treatment of Atrioventricular Block.

G. FRIESE AND R. THORSPECKEN: *Deutsche med. Wchnschr.*, 86: 1045, 1961 (German).

Isopropylnoradrenaline (IPNA) has been used successfully for the treatment of disturbances of atrioventricular conduction, but it has certain disadvantages. It must be given sublingually, because it is destroyed in the gastrointestinal tract, and its solution is not stable. It is therefore not suitable for parenteral administration. This article is a report on a new preparation "Alupent" which is chemically almost identical with IPNA, the only difference being the position of one OH-group. This product can be given orally, and it forms a stable solution, permitting intramuscular and intravenous injection.

Preliminary tests on 10 healthy volunteers revealed that 20 mg. of Alupent increased the heart rate about as much as 10 mg. of IPNA, although the onset of action was slower. No essential side effects were noted.

Eight patients with complete atrioventricular block were treated with the new drug. In two patients a normal sinus rhythm returned, and in one patient the complete block was changed to a 2:1 block. In four cases the heart block remained unchanged but the heart rate increased enough to prevent Adams-Stokes attacks. One patient did not respond, and a change of his medication to IPNA also had no effect.

Another group of eight patients included four cases of incomplete atrioventricular block, two cases of sinoauricular block and two cases of bradycardia with Adams-Stokes syndrome. Four of these responded with a normal sinus rhythm, two with a sufficient increase of the heart rate to eliminate attacks of syncope, and in two there was no improvement.

One patient who was about to be supplied with an electric pacemaker developed cardiac arrest during intubation. Immediate intravenous injection of 0.25 mg. of Alupent resulted in resumption of cardiac function and the operation was completed successfully.

In the first 16 patients the daily oral dose of Alupent varied between 30 and 240 mg. divided into single doses of 5 to 20 mg. When used intramuscularly the single dose was 0.5 to 1.0 mg., and in rare cases it was used intravenously either as a single injection of 0.25 mg. or as a drip (5-10 mg. in 250 c.c. of fluid).

The author stated that his results with this small group of patients were being reported because he considers that Alupent represents an improvement over IPNA. KATHERINE E. RICHTER

Cerebral Fat-Embolism Successfully Treated by Carbon-Dioxide Inhalation.

B. BROOM: *Lancet*, 1: 1324, 1961.

A case of cerebral fat-embolism, in which the patient made a complete recovery, is reported.

The patient, a 33-year-old wood machinist, was deeply comatose with decerebrate rigidity before he was given 20% carbon dioxide in the form of a mixture of 4 litres of oxygen and I litre of carbon dioxide by inhalation through an endotracheal tube, for five-and-one-half hours.

The mortality from cerebral fat-embolism may be very high, rates of 61.4% and 75% being reported by two other authors. In view of the poor prognosis of cerebral fat-embolism with coma, the effect of carbon-dioxide inhalation was tried. Carbon dioxide is the most potent agent known in increasing the cerebral blood flow; it seemed that maximal vasodilatation might help to combat the effects of the emboli and to speed the patient's recovery.

Although opinions differ as to the largest amount of carbon dioxide that should be inhaled, the author believes that more intensive carbon-dioxide therapy than is usually employed might be considered when its use is indicated. FRANCES LETTAU